

---

# Outcomes of asymptomatic and symptomatic Rheumatic Heart Disease

---

Dr Liesl Joanna Zühlke  
MBChB DCH FCPaeds Cert Card MPH FESC



Dissertation Presented for the Degree of  
Doctor of Philosophy in the Department of Paediatrics  
School of Child and Adolescent Health  
Faculty of Health Sciences  
UNIVERSITY OF CAPE TOWN

November 2015

Supervisor:  
Professor Bongani Mayosi  
Co-Supervisor:  
Associate Professor Mark Engel

The copyright of this thesis vests in the author. No quotation from it or information derived from it is to be published without full acknowledgement of the source. The thesis is to be used for private study or non-commercial research purposes only.

Published by the University of Cape Town (UCT) in terms of the non-exclusive license granted to UCT by the author.

---

## **Outcomes of asymptomatic and symptomatic Rheumatic Heart Disease**

## Declaration

I, Liesl Joanna Zühlke hereby grant the University of Cape Town free license to reproduce the above thesis in whole or part, for the purpose of research.

I declare that:

The above thesis is my own unaided work, in both concept and execution and, apart from the normal guidance from my supervisor, I have received no assistance except as stated below:

Assistance was received as indicated in the Acknowledgments

Word Count: 58057 (46617 excluding appendices)

This thesis is my own work and has not been submitted in any form for another degree or diploma at any university or other institution of tertiary education. Information derived from the published or unpublished work of others has been acknowledged in the text and a list of references given.

I am now presenting the thesis for examination for the degree of PhD.

Signed by candidate

Signature Removed

Signature

10 March 2015

Date

---

## Acknowledgements

My sincerest thanks and appreciation to the following persons:

Colleagues and collaborators on the various studies and papers presented in this thesis:

Professor Andrew Steer and Dr David Watkins

All the investigators, steering committee members, data managers and coordinating staff in all the countries involved in REMEDY. A particular thanks to Professor Karthikeyan, the PHRI team members Pam Mackie and Sumathy Rangarajan, and all the Cape Town co-ordinating staff.

My colleagues at Red Cross Children's Hospital Department of Paediatric Cardiology, especially Drs John Lawrenson and Rik De Decker for their support and encouragement. A special mention to Drs Kathie Walker and Wendy Matthiassen for their tireless commitment to RHD patients over several decades.

My mentors: Professor Bongani Mayosi, Professor Jonathan Carapetis, Professor Heather Zar, and Professor Landon Myer – collectively you have inspired, encouraged and supported me beyond measure over the past years.

Statistician Katya Mauff for her amazing patience, help and statistical prowess, and for bringing fun and aha! moments to Thursday mornings.

Professor Mark Engel and the ASAP team: PrheDICT – Carolise Lemmer, Simpiwe Nkepu, Marnie van der Waal; REMEDY – Rezeen Daniels, Peggy Mgwai, Alexia Joachim, Alet Meiring, Veronica Francis, Unita September, Lwazi Mhlanti, Janine Saaiman, Felicia Gili, Dylan Barth. Thank you to you all for your hard work, dedication and commitment to the projects and thus to the patients.

My dearest friend Alexia Joachim, who has consistently cared for my wellbeing throughout this process and whose friendship I continue to prize greatly.

My co-supervisor, office companion, friend and colleague, Professor Mark Engel. We have travelled an exciting road together – may God continue to guide your path – thank you for your support, invaluable help and guidance. This thesis is a product of your input in so many ways.

My supervisor, Professor Bongani Mayosi for encouraging my research career, and for his enthusiasm, positivity, expert guidance and leadership.

Stephanie Edwards, who has helped me to balance so many balls in the air, and who cared for our children and our home in the process.

My amazing family for your unrelenting support: my mother, Linda Hendricks; sisters, Wendy and Samantha; brothers-in-law, Michael and Dean; and nieces and nephew, Carolyn, Zara and Ethan: the wonderful Zupaburys.

I would also like to thank and acknowledge the funders of my research, salary and project support: the Discovery Academic Fellowship Award, the NIH Fogarty Fellowship, the Thrasher Foundation, CIDRI (Clinical Infectious Disease Research Initiative) and the Hamilton Naki Clinical Scholarship Programme, funded by Netcare Limited.

My studies were funded by the NIH Fogarty Fellowship, the Thrasher Foundation, Wellcome CIDRI – Clinical Infectious Disease Research Initiative, the Medical Research Council, Else Kroner Frassenius Foundation, the World Heart Federation, Novartis, and the University of Cape Town. This thesis would not have been possible without the support, love and extremely patient understanding of my dear husband, Alexander, and our beloved children, Gabriel and Eli. You are and will always be the greatest joy in my life.

“You raise me up, so I can stand on mountains;  
You raise me up to walk on stormy seas;  
I am strong when I am on your shoulders;  
You raise me up to more than I can be”

I dedicate this thesis to the memory of my father, Alfred William Hendricks, and my grandmother, Eva Davids – two formidable giants who believed in education and the strength of dreams.

Father almighty,  
I offer myself to you  
As a living sacrifice  
In Jesus Christ our Lord.  
Send me out into the world  
In the power of the Holy Spirit  
To live and work  
To your praise and glory.

---

## Publications arising from this thesis

1. **ZÜHLKE, L.** & MAYOSI, B. M. 2013. Echocardiographic screening for subclinical rheumatic heart disease remains a research tool pending studies of impact on prognosis. *Curr Cardiol Rep*, 15, 343.
2. **ZÜHLKE, L. J.** & STEER, A. C. 2013. Estimates of the Global Burden of Rheumatic Heart Disease. *Global Heart*, 8, 189-195.
3. **ZÜHLKE, L.**, WATKINS, D. & ENGEL, M. E. 2014b. Incidence, prevalence and outcomes of rheumatic heart disease in South Africa: a systematic review protocol. *BMJ Open*, 10;4(6):e004844.
4. **ZÜHLKE, L.**, ENGEL, M. E., KARTHIKEYAN, G., RANGARAJAN, S., MACKIE, P., CUPIDO, B., MAUFF, K., ISLAM, S., JOACHIM, A., DANIELS, R., FRANCIS, V., OGENDO, S., GITURA, B., MONDO, C., OKELLO, E., LWABI, P., AL-KEBSI, M. M., HUGO-HAMMAN, C., SHETA, S. S., HAILEAMLAK, A., DANIEL, W., GOSHU, D. Y., ABDISSA, S. G., DESTA, A. G., SHASHO, B. A., BEGNA, D. M., ELSAYED, A., IBRAHIM, A. S., MUSUKU, J., BODE-THOMAS, F., OKEAHIALAM, B. N., IGE, O., SUTTON, C., MISRA, R., ABUL FADL, A., KENNEDY, N., DAMASCENO, A., SANI, M., OGAH, O. S., OLUNUGA, T., ELHASSAN, H. H., MOCUMBI, A. O., ADEOYE, A. M., MNTLA, P., OJJI, D., MUCUMBITSI, J., TEO, K., YUSUF, S. & MAYOSI, B. M. 2014. Characteristics, complications, and gaps in evidence-based interventions in rheumatic heart disease: the Global Rheumatic Heart Disease Registry (the REMEDY study). *Eur Heart J*. Nov 25. pii: ehu449. [Epub ahead of print]

## Abstract presented at a congress with data from this thesis

1. **ZÜHLKE, L. J.**, KARTHIKEYAN, G., ENGEL, M., CUPIDO, B., JOACHIM, A., DANIELS, R., RANGARAJAN, S., TEO, K., YUSUF, S. & MAYOSI, B. 2012. The Rheumatic Heart Disease Global Registry (REMEDY) study: preliminary report. *Circulation*, 125, E723-E723.

# **Outcomes of asymptomatic and symptomatic Rheumatic Heart Disease**

## **Abstract**

Rheumatic Heart Disease (RHD) is a leading cause of heart disease in children and young adults in the developing world, with significant associated morbidity and mortality. Early secondary prophylaxis may retard the deleterious progression from its antecedent, acute rheumatic fever to permanent heart valve damage, and thus several echocardiographic screening programmes to detect asymptomatic RHD and institute early prophylaxis have been conducted. While effective interventions are available for ameliorating the effects of RHD, research on their use in different settings is scant. Key questions remain regarding the natural history of asymptomatic RHD and the optimal method for early detection. In addition, there is a lack of contemporary estimates of mortality and morbidity among the symptomatic population in the developing world.

The primary purpose of the thesis was to determine the outcomes of asymptomatic and symptomatic RHD. More specifically, I sought to quantify the incidence, prevalence and outcomes of RHD in South Africa over the past two decades, determine the natural history of asymptomatic RHD and validate a focused protocol for screening in schoolchildren from Cape Town. In addition, I determined the baseline characteristics, prevalent sequelae and gaps in evidence-based implementation in children and adults from 14 developing countries. Finally, I investigated the independent predictors for mortality and morbidity of RHD over a two-year period in patients from Cape Town, South Africa.

My thesis has five key findings. Firstly, a systematic review of the literature showed that the incidence and prevalence of RHD over the past two decades in South Africa remains high, although there is evidence of falling cause-specific mortality at a population level. Secondly, asymptomatic RHD has a variable natural history that ranges from regression to a normal state, to persistence of disease, and progression to symptomatic RHD. Thirdly, a focused hand-held echocardiography protocol shows promising levels of sensitivity and specificity for detecting subclinical RHD. Fourthly, the baseline data from the global rheumatic heart disease registry demonstrates significant gaps in the implementation of medical and surgical interventions of proven effectiveness in low- and middle-income countries. Finally, the annual mortality rate for children and adults with RHD in Cape Town over a two-year period is 4.1% with cardiovascular events occurring at a rate of 0.18 events per patient per year. The findings encapsulated in this thesis have important implications for policy, practice and research related to the management of asymptomatic and symptomatic RHD in the world.



---

# Table of Contents

<b>Declaration</b>	3
<b>Acknowledgements</b>	4
<b>Publications arising from this thesis</b>	6
<b>Abstract</b>	7
<b>List of Figures</b>	12
<b>List of Tables</b>	13
1 Introduction and review of the literature	16
1.1 Global Burden of Disease	17
1.1.1 Burden of disease estimates: Existing population-based studies	17
1.1.2 Extrapolation of data	20
1.1.3 Estimating the burden of rheumatic heart disease causing symptomatic disease	21
1.1.4 Defining the true burden of disease due to rheumatic fever and rheumatic heart disease	23
1.2 The South African situation: Incidence, prevalence and complications of rheumatic heart disease in the current era	24
1.2.1 Incidence of acute rheumatic fever and rheumatic heart disease	24
1.2.2 Prevalence of rheumatic heart disease in South Africa	25
1.2.3 Outcomes of rheumatic heart disease in South Africa	26
1.3 Natural history of asymptomatic rheumatic heart disease	27
1.3.1 Natural history of subclinical carditis in acute rheumatic fever	29
1.3.2 Progression of echocardiographic changes detected as part of auscultation-based screening	30
1.3.3 Screening using portable echocardiography	31
1.3.4 Progression of echocardiographic changes detected as part of screening	35
1.4 Alternate modalities for screening for asymptomatic rheumatic heart disease	37
1.4.1 Alternate protocols for screening using echocardiography	37
1.4.2 Computer-assisted auscultation	39
1.4.3 Hand-held echocardiography	41
1.5 Baseline characteristics of symptomatic disease	42
1.5.1 Clinical characteristics in the context of a global transition	43
1.6 Sequelae of rheumatic heart disease	44
1.7 Summary and rationale for this thesis	46
1.8 A new model of rheumatic heart disease: The RHD pyramid	47
1.9 Specific aims of the thesis	48

2	Methods .....	49
2.1	Global strategies to eliminate rheumatic heart disease in the 21 <sup>st</sup> century .....	49
2.2	Study 1: Systematic review of incidence, prevalence and outcomes of rheumatic heart disease .....	50
2.2.1	Methods.....	51
2.2.2	Inclusion and exclusion criteria .....	51
2.2.3	Search strategy.....	52
2.2.4	Data extraction.....	53
2.2.5	Quality assessment.....	55
2.2.6	Risk of bias assessment.....	55
2.2.7	Data synthesis.....	57
2.2.8	Presenting and reporting of results.....	57
2.2.9	Outcomes.....	57
2.3	Study 2: The natural history of asymptomatic rheumatic heart disease detected by echocardiography in schoolchildren .....	58
2.3.1	The ASAP Programme .....	58
2.3.2	Setting .....	59
2.3.3	Participants.....	61
2.3.4	Variables and measurement .....	61
2.3.5	Bias .....	62
2.3.6	Study design.....	62
2.3.7	Statistical methods .....	63
2.3.8	Aims .....	63
2.4	Study 3: Alternative modalities of screening for asymptomatic rheumatic heart disease.....	63
2.4.1	Study population.....	66
2.4.2	Methods.....	68
2.4.3	Statistical methods .....	69
2.4.4	Aims .....	70
2.5	Studies 4 and 5: The clinical characteristics, treatment and outcome of symptomatic rheumatic heart disease – The Global Rheumatic Heart Disease Registry (The REMEDY Study).....	71
2.5.1	Study design and participants.....	71
2.5.2	Study organisation and data collection .....	71
2.5.3	Statistical methods .....	72
2.5.4	Specific objectives of the REMEDY study: Baseline .....	74
2.5.5	Specific objectives of the REMEDY study: Follow-up.....	75
2.6	Summary.....	75

---

3	Study 1: Incidence, prevalence and outcomes of rheumatic heart disease in South Africa: A systematic review of contemporary studies .....	76
3.1	Abstract .....	76
3.2	Introduction.....	77
3.3	Methods.....	77
3.4	Description of studies .....	78
3.5	Results.....	86
3.6	Discussion.....	94
3.7	Conclusion .....	96
4	Study 2: The natural history of asymptomatic rheumatic heart disease.....	97
4.1	Abstract .....	97
4.2	Introduction.....	98
4.3	Methods.....	99
4.4	Results.....	99
4.5	Discussion.....	104
4.6	Conclusion .....	106
5	Study 3: Alternate screening modalities of detecting rheumatic heart disease in asymptomatic school children.....	107
5.1	Abstract .....	107
5.2	Introduction.....	108
5.3	Methods.....	109
5.4	Results.....	109
5.5	Discussion.....	113
5.6	Conclusion .....	116
6	Study 4: Baseline characteristics, complications, and gaps in evidence-based interventions in 3,343 children and adults with rheumatic heart disease .....	117
6.1	Abstract .....	117
6.2	Introduction.....	118
6.3	Methods.....	118
6.4	Results.....	119
6.5	Discussion.....	129
6.6	Conclusion .....	131

7	Study 5: Contemporary estimates of morbidity and mortality of rheumatic heart disease in South Africa: Outcomes from the Cape Town component of the global rheumatic heart disease registry .....	132
7.1	Abstract .....	132
7.2	Introduction.....	133
7.3	Methods.....	133
7.4	Results.....	134
7.5	Discussion .....	146
7.6	Conclusion .....	149
8	Summary and conclusions.....	150
1.	Principal findings .....	150
2.	Implications for policy and practice.....	151
3.	Implications for future research .....	152
9	References.....	154
10	Appendices .....	169
10.1	CT IRB Ethics approval letters .....	170
10.2	Study 1: Meta-analysis of Observational Studies in Epidemiology (MOOSE) checklist .....	173
10.3	Study 1: Data extraction form.....	175
10.4	Study 2: Case record form .....	185
10.5	Study 3: Case record form .....	192
10.6	Study 4: REMEDY Registration Form .....	197
10.7	Study 4: REMEDY Baseline form .....	198
10.8	Study 4: List of participating sites and country .....	208
10.9	Study 5: 12 and 24 month outcomes .....	211
10.10	Study 4 and 5 : REMEDY Manual of operations.....	219

---

## List of Figures

Figure 1.1. Prevalence of rheumatic heart disease .....	18
Figure 1.2. Trends in the incidence of acute rheumatic fever and prevalence of rheumatic heart disease .....	19
Figure 1.3. Estimates of acute rheumatic fever, rheumatic heart disease and mortality .....	21
Figure 1.4. Countries with established cardiac surgery programmes .....	22
Figure 1.5. Annual specific incidence rate (temporal trend) of first attack of acute rheumatic fever.....	24
Figure 1.6. Factors affecting aetiology of valvular heart disease over the past half century .....	26
Figure 1.7. Clinical observations of the events preceding the appearance of rheumatic fever.....	28
Figure 1.8. The causal pathway to rheumatic heart disease and points of intervention.....	29
Figure 1.9. Prevalence of non-ejection clicks and mitral systolic murmurs .....	30
Figure 1.10. Features relating to auscultation of the 1976 group compared with those in 1972.....	31
Figure 1.11. RHD detected amongst schoolchildren by means of echo-based screening in Africa.....	32
Figure 1.12. Comparison of rheumatic heart disease prevalence, utilizing different criteria for the same dataset.....	33
Figure 1.13. Screening using auscultation versus echocardiography.....	40
Figure 1.14. Prevalence of rheumatic heart disease by gender .....	42
Figure 1.15. A population model for assessing and reporting burden of rheumatic heart disease incorporating asymptomatic and symptomatic disease .....	47
Figure 2.1. Zargis user interface in the case of an abnormal murmur being detected.....	68
Figure 2.2. Screen positive mitral regurgitation jet .....	69
Figure 3.1. Flow diagram of study selection.....	79
Figure 3.2. Study-specific risk of bias scores .....	84
Figure 3.3. Risk of bias.....	85
Figure 3.4. Pre-operative atrial fibrillation.....	90
Figure 3.5. Early post-operative mortality.....	91
Figure 3.6. Rheumatic heart disease mortality rate, 1997-2012 .....	93
<b>Figure 4.1. Percentage of follow-up .....</b>	<b>100</b>
Figure 4.2. Natural history of asymptomatic rheumatic heart disease .....	102
Figure 4.3. Reports of natural history of asymptomatic rheumatic heart disease.....	105
Figure 5.1 Cases identified using different screening methods .....	113
Figure 6.1. Age and gender distribution of 3,343 children and adults with rheumatic heart disease.....	119
Figure 6.2. Utilisation of valve surgery and valvuloplasty from different income category countries.....	122
Figure 6.3. The pattern of native rheumatic valve disease in 2,475 children and adults .....	124
Figure 6.4. Severity of all rheumatic valve lesions with echocardiograms at enrolment.....	125
Figure 6.5. Adherence to penicillin secondary prophylaxis .....	127
Figure 6.6. INR-categories at enrolment.....	127
Figure 7.1. Age and gender distribution.....	134
Figure 7.2. Findings on history and clinical examination.....	137
Figure 7.3. Kaplan-Meier survival analysis of study patients compared to match population controls .....	138
Figure 7.4. Cumulative mortality with decreased ejection fraction at enrolment .....	139
Figure 7.5. Cumulative mortality after cardiac failure at enrolment .....	144
Figure 7.6. Comparison of cumulative percentage all-cause mortality for those with or without episodes of cardiac failure.....	145

## List of Tables

Table 1.1. Prevalence using clinical auscultation: South African studies .....	25
Table 1.2. World Heart Federation criteria for echocardiographic diagnosis of rheumatic heart disease .....	34
Table 1.3. Short-term follow-up studies: Study characteristics and outcomes .....	36
Table 1.4. Alternate methods of screening for rheumatic heart disease .....	38
Table 2.1. Search strategy .....	54
Table 2.2. Design-specific criteria for risk of bias assessment .....	56
Table 2.3. Reclassification of all definite and probable disease. ....	60
Table 2.4. Alternate methods of screening for rheumatic heart disease .....	65
Table 2.5. World Heart Federation Guidelines .....	67
Table 2.6. Visit schedules and recommended study procedures .....	72
Table 2.7. REMEDY event definitions.....	73
Table 3.1. Excluded studies.....	80
Table 3.2. Included studies.....	81
Table 3.3. Characteristics of included studies.....	82
Table 3.4. Incidence per 100,000 population per age stratum.....	86
Table 3.5. Demographics and mortality of rheumatic heart disease patients admitted for acute heart failure .....	87
Table 3.6. Fatal and non-fatal outcomes in surgical reviews .....	89
Table 3.7. Summary of Statistics South Africa reports .....	92
<b>Table 4.1. Classification of abnormal echocardiograms at enrolment .....</b>	<b>99</b>
Table 4.2. Characteristics of the learners at follow-up visit .....	101
Table 4.3. Echocardiographic features associated with progression or persistence of lesions.....	103
Table 5.1. Test characteristics for detecting subclinical rheumatic heart disease .....	110
Table 5.2. Performance characteristics of alternate modalities to identify definite rheumatic heart disease .....	112
Table 5.3. Performance characteristics of alternate modalities in identifying borderline rheumatic heart disease.....	112
Table 5.4. Classification of definite and borderline cases .....	114
Table 6.1. Demographic characteristics of 3,343 children and adults with rheumatic heart disease .....	120
Table 6.2. Clinical characteristics of 3,343 children and adults with rheumatic heart disease.....	121
Table 6.3. Use of anti-thrombotic medication and quality of anticoagulation in patients with an indication for oral anticoagulant therapy .....	128
Table 7.1. Baseline characteristics .....	135
Table 7.2. Baseline clinical, past medical and surgical history and echocardiographic characteristics .....	136
Table 7.3. Univariable and multivariable models for all-cause mortality .....	140
Table 7.4. Cardiovascular events and interventions.....	141
Table 7.5. Models for adverse cardiovascular events and all-cause death .....	142
Table 7.6. Models for all-cause mortality: Enrolment and subsequent variables .....	143
Table 7.7. Previously identified independent risk factors: Pre and post-intervention comparison .....	146

---

## List of Abbreviations and Acronyms

ACC	American College of Cardiology
AF	Atrial fibrillation
AHA	American Heart Association
AMVL	Anterior mitral valve leaflet
AO	Aorta
AR	Aortic regurgitation
ARF	Acute rheumatic fever
ASAP	Awareness Surveillance Advocacy Prevention
AV	Aortic valve
AVD	Aortic valve disease
CAA	Computer-assisted auscultation
CCF	Congestive cardiac failure
CHB	Chris Hani Baragwanath Hospital
CHF	Congestive Heart Failure
CI	Confidence interval
CRF	Case record forms
ECG	Electrocardiograph
EF	Ejection fraction
ES	Effect size
FOCUS	A <u>F</u> ocused method <u>U</u> tilizing hand-held echocardiography in <u>S</u> creening for RHD
GAS	Group A streptococcus
GSH	Groote Schuur Hospital
HIV	Human Immunodeficiency Virus
IE	Infective endocarditis
INR	International Normalised Ratio
IQR	Interquartile range
LA	Left atrium
LIC	Low-income country
LMIC	Lower-middle income country
LR-	Negative likelihood ratio test
LR+	Positive likelihood ratio test
LVEDD	Left ventricular end diastolic diameter
LVEF	Left ventricular ejection fraction
MAVD	Mixed aortic valve disease
MMAVD	Mixed mitral and aortic valve disease

MMVD	Mixed mitral valve disease
MOOSE	Meta-analysis of observational studies in epidemiology
MR	Mitral regurgitation
MS	Mitral stenosis
MV	Mitral valve
NIH	National Institutes of Health
NPV	Negative predictive value
NR	Not reported
NYHA	New York Heart Association
OAC	Oral anticoagulant
OR	Odds ratio
PACER	Prognostic indicators and predictors for Adverse Cardiovascular Events associated with RHD
PPV	Positive predictive value
PR	Pulmonary regurgitation
PS	Pulmonary stenosis
PVT	Prosthetic valve thrombosis
Re-LY	The Randomised Evaluation of Long-Term Anticoagulation Therapy in AF
REMEDY	Global Rheumatic Heart Disease registry study
RHD	Rheumatic heart disease
RHEUMATIC	Rheumatic heart echo utilisation and monitoring actuarial trends in Indian children
RHF	Right heart failure
SD	Standard deviation
TBH	Tygerberg Hospital
THESUS-HF	The Sub-Saharan Africa Survey of Heart Failure
TIA	Transient ischaemic attack
TR	Tricuspid regurgitation
TS	Tricuspid stenosis
UMIC	Upper-middle income country
WHF	World Heart Federation
WHO	World Health Organisation



## **1 Introduction and review of the literature**

Rheumatic Heart Disease (RHD), one of the consequences of Group A streptococcus (GAS) infection, remains a leading cause of heart disease in children and young adults in the developing world, with an annual mortality comparable to that of rotavirus and significant associated morbidity. However, if diagnosed early enough with timely institution of secondary prophylaxis, the deleterious progression to permanent heart valve damage due to recurrent episodes of acute rheumatic fever (ARF) need not occur. This argument has led to the launch of a multitude of echocardiographic screening programmes to document the prevalence of subclinical disease and to institute early therapy in affected individuals (Marijon et al., 2012; Saxena et al., 2013). So far, however, only short-term studies exist with regard to the use of screening to detect subclinical RHD (Beaton et al., 2014b; Roberts et al., 2013a; Zühlke and Mayosi, 2013). In addition, screening in rural and low-resource settings requires a different approach, before large-scale screening in such areas can be advocated. Retrospective studies show that RHD is associated with high mortality and substantial morbidity due to sequelae such as congestive heart failure (CHF), stroke and infective endocarditis (IE) (Diao et al., 2011; Gunther et al., 2006). Yet, contemporary estimates of the burden of disease, especially from different areas in the developing world where this disease is endemic, such as South Africa, are scant and largely retrospective in nature. However, we require these estimates of outcomes of clinical disease in order to quantify the mortality and morbidity associated with the disease in the current era and to identify the characteristics of affected patients.

This thesis focuses on exploring the outcomes of asymptomatic and symptomatic RHD within the context of increasing numbers of screening programmes and a high burden of clinical disease. In this introduction, I summarise the current knowledge related to disease estimates for RHD, and the morbidity and mortality associated with RHD, with a particular focus on South Africa. I also review current information regarding the natural history of asymptomatic RHD, screening for asymptomatic RHD, and the use of alternate screening modalities. In conclusion, I précis the current literature, present a new model of integrating asymptomatic and symptomatic RHD, and list the aims and objectives of this thesis.

## **1.1 Global Burden of Disease**

In this section, I will be summarising the current knowledge related to global burden of disease estimates, focusing on rheumatic heart disease (RHD) and its consequences.

Acute rheumatic fever (ARF) and its sequel, RHD, continue to cause significant morbidity and mortality in developing countries and for decades have been under-recognised as a global health problem. There are a number of reasons for this under-recognition. Firstly, it is attributable to the competing heavy burden of infectious disease mortality in young children due to HIV, malaria, tuberculosis, diarrhoeal disease and pneumonia. Secondly, there has been an impressive decline in the incidence of ARF in industrialised countries over the second half of the previous century, such that ARF/RHD are uncommon in these countries today and are thus no longer priority diseases. Finally, the paucity of good quality and widely collected epidemiological data from developing countries has also contributed to the under-recognition of these diseases (Tibazarwa et al., 2008). Recently, however, awareness of RHD has increased because a number of countries with high disease burdens have prioritised control of the disease; this has re-invigorated regional initiatives directed at the control of RHD, particularly in the Pacific region and in Africa, and advocacy efforts have been led by international bodies, such as the World Heart Federation (WHF). Central to this increased awareness have been updated and persuasive global morbidity and mortality figures (Carapetis et al., 2005; Jackson et al., 2011; Seckeler and Hoke, 2011). Recent directives from the World Health Organisation (WHO) and the WHF have pledged to decrease the number of deaths due to non-communicable diseases by 25% by 2025 (Smith et al., 2012). RHD is one disease where this target may indeed be achievable because relatively inexpensive, proven and effective control strategies exist that can lead to reductions in deaths, especially in those below the age of 25 years (Ralston, 2012; Wyber et al., 2014).

### **1.1.1 Burden of disease estimates: Existing population-based studies**

In 2005, a summary report, commissioned by the WHO, was released on the global burden of Group A streptococcal disease; it encapsulated population-based data relating to ARF and RHD that had been published between 1985 and 2005 (Carapetis et al., 2005). This report calculated the prevalence of RHD and the incidence of ARF and of new cases of RHD across multiple geopolitical regions. It found an overall global burden of 471,000 annual cases of ARF, with the incidence of ARF ranging from 10 cases per 100,000 children aged 5 to 15 years in industrialised

countries to 374 cases per 100,000 in the Pacific region. The overall burden of RHD was estimated to be 15.6 million prevalent cases, with 282,000 new cases and over 233,000 deaths per year (Figure 1.1). As the authors noted in their publication (Carapetis et al., 2005), there are some important caveats in these estimates, relating to the number of available studies, the extrapolations made to reach all-ages estimates and global mortality estimates, as well as the significance of the echocardiographic detection of RHD in screening studies. Three reports subsequently reviewed the global burden of ARF and RHD: two were published in 2011 (Jackson et al., 2011; Seckeler and Hoke, 2011), and a third, part of the Global Burden of Disease 2010 Study, was published in 2012 (Murray et al., 2012a).

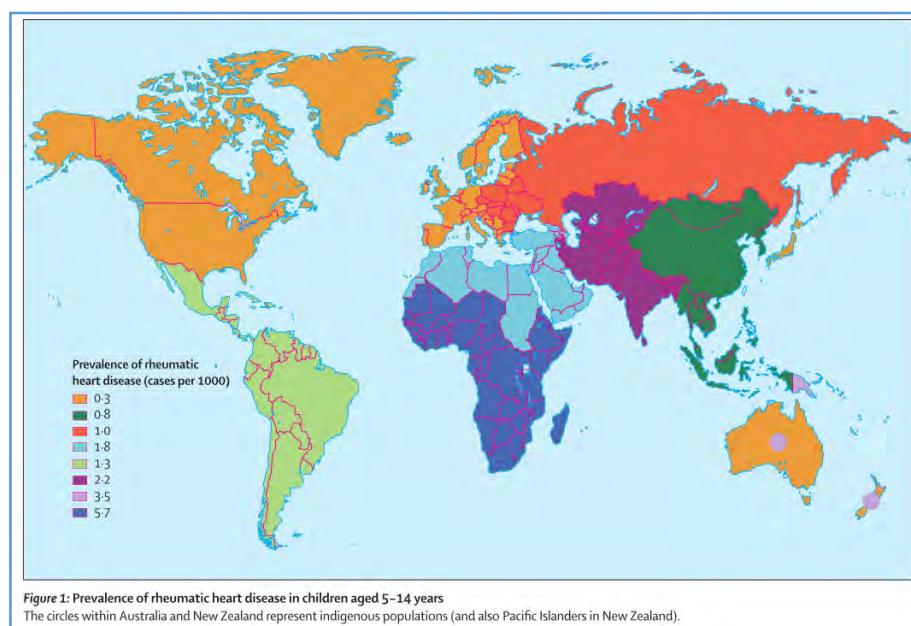


Figure 1.1. Prevalence of rheumatic heart disease  
(Carapetis et al., 2005)

The first study added several new datasets, extracted from 57 studies of RHD in multiple geographic regions of the world; it used a clearly defined systematic review design, included only studies in which RHD was diagnosed by means of an echocardiogram (Jaffe et al., 1988), and incorporated vital registration data from the WHO. Mortality rates were calculated by using the most recent WHO population data, but countries were included only if death reports had been completed for more than 90% of the country's total deaths. The study concluded that there is considerable global variation in ARF incidence and RHD prevalence, with the sub-Saharan African and Asian-Pacific regions identified as high disease burden areas. However, the contribution of distal sequelae of RHD (congestive cardiac failure [CCF], IE, atrial fibrillation [AF] and stroke) was not addressed in that study.

The second study (Seckeler and Hoke, 2011) observed that the overall global prevalence of RHD appeared to be increasing, while the incidence of ARF was decreasing in many parts of the world, including in Africa (Figure 1.2). The authors explained this apparent discrepancy by attributing it to reporting bias, namely, that the systematic reporting of ARF in many countries had decreased at the same time that the ascertainment of RHD cases had increased because of RHD screening studies.

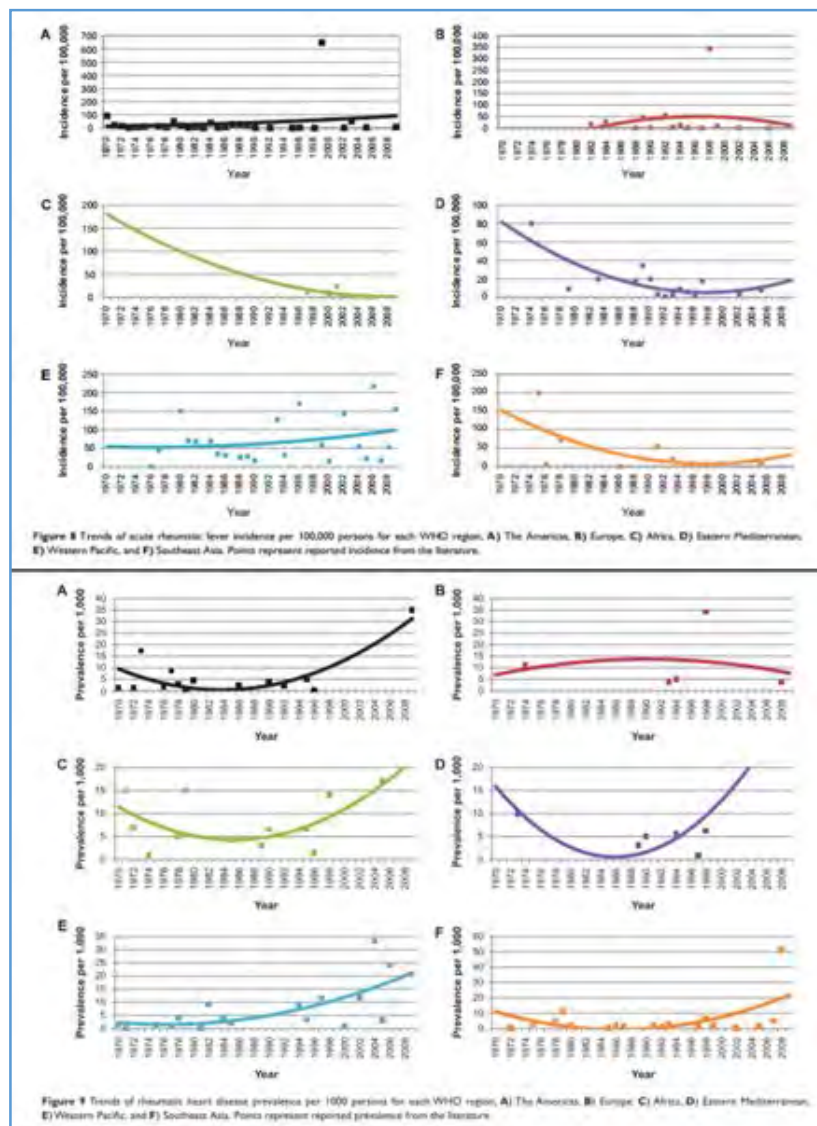


Figure 1.2. Trends in the incidence of acute rheumatic fever and prevalence of rheumatic heart disease (Seckeler and Hoke, 2011)

The third document, the recently published Global Burden of Disease 2010 Study (2010), reported that the number of years lived with disability due to RHD worldwide was estimated at 1,430 in

2010 (95% confidence intervals [CI] 944 to 2067), a figure that represents up to one fourth of all neoplasms (Vos et al., 2012). Lozano reported 345,100 deaths due to RHD in 2010, representing a 25.4% reduction compared with those occurring in 1990, with an age-standardised death rate of 5.2 per 100,000. This represents a 53.1% reduction in the death rate, when compared with the number of deaths that occurred in 1990 (Lozano et al., 2012). It is necessary to re-analyse this data, however, due to uncertainties regarding their accuracy. Of particular concern were the clear inconsistencies relating to the epidemiology of the disease, the age groups that are most at risk, and the extreme paucity of incident and mortality data from developing countries. Moreover, a recent report from the Northern Territories in Australia reported little evidence of a decline in the incidence of ARF or RHD (Lawrence et al., 2013).

While the publication of these data filled an important gap in the literature, some significant limitations remained. The major limitation was the poor-quality data from some of the most-affected regions, especially relating to mortality, with only a single publication available from some regions of importance. The lack of incident ARF data is a particular concern (Milne et al., 2012a). The paucity of data meant that prevalence figures from a small number of studies in a limited number of countries were extrapolated to whole regions, thereby ignoring the considerable differences in disease burden that are likely to exist between countries, and indeed between states and districts in many of the larger countries. For example, many prevalence studies of RHD cited in this study were conducted in urban and peri-urban populations, while it is known that the prevalence of RHD is often higher in rural areas (Longo-Mbenza et al., 1998; Tantchou Tchoumi and Butera, 2009). Thus, there is a very clear need for contemporary disease estimates from developing countries, in particular from countries with less robust central data collection methods.

### **1.1.2 Extrapolation of data**

RHD is a cumulative disease, and thus there are more people aged over 15 years with the disease than those under 15 years. To extrapolate to the all-age estimates of RHD, the authors of both the 2005 study and the first of the 2011 studies used a multiplication factor of between 5.5 and 7.2, based on the published data from two other studies (Agarwal et al., 1995; Carapetis et al., 2000). Although they were careful to underestimate rather than overestimate, these extrapolated figures are clearly subject to error. Therefore, the annual number of global deaths due to RHD estimated in these studies is likely to be an underestimate of the true situation in endemic regions; for example, in Pakistan and Ethiopia, the mortality rate is as high as 6.8% and 12.1% respectively

(Gunther et al., 2006; Jackson et al., 2011). Ideally, local mortality rates should be applied to local RHD prevalence rates in order to calculate overall mortality. Recently, a local publication attempted to estimate the burden of mortality by using the low and likely estimates as depicted in Figure 1.3; yet it is clear that we need real data (Hewitson and Zilla, 2010).

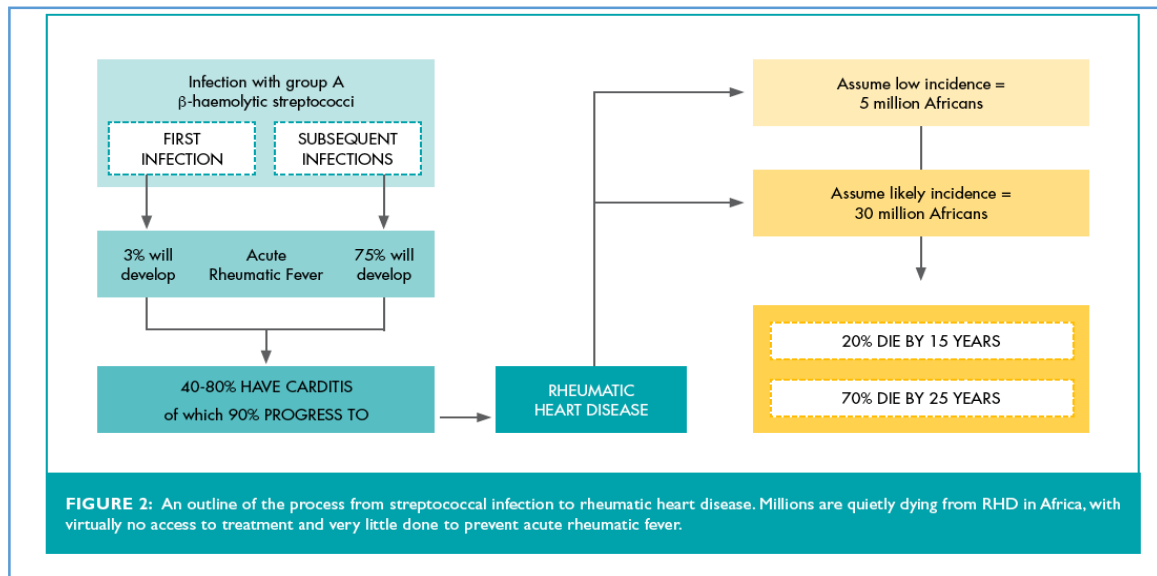


Figure 1.3. Estimates of acute rheumatic fever, rheumatic heart disease and mortality (Hewitson and Zilla, 2010)

### 1.1.3 Estimating the burden of rheumatic heart disease causing symptomatic disease

Very few reports have described the clinical characterisation of cases on RHD registers and incident cases presenting at hospitals. A study arising from a clinical registry in Soweto, South Africa, estimated the annual incidence of new cases of RHD in the region to be 23.5 cases per 100,000 people aged over 14 years (Sliwa et al., 2010). This study highlighted the severity of disease in patients who were presenting for the first time with symptomatic RHD; the majority of patients presented with impaired systolic function, elevated right ventricular systolic pressure (>35 mmHg) and AF, and surgery was necessary in 22% of these cases. The study also highlighted the relevance of the complications of RHD; 26% of cases were admitted within 30 months of initial diagnosis for suspected IE.

RHD as a cause of foetal and maternal morbidity and mortality has hitherto been underestimated. In a study of pregnant women with RHD in Senegal, the maternal mortality rate was 34%, peaking at 54% for women with mitral stenosis (Diao et al., 2011). In South Africa, 0.6% of pregnant

women had pre-existing cardiac abnormalities, with RHD being the most common cardiac problem (Watkins et al., 2012). In the Pacific, RHD is a leading cause of maternal mortality; for instance, in a study from Fiji, the prevalence of RHD in pregnant women was 0.2% (Steer et al., 2009a).

Significant challenges exist in the provision of cardiac surgery in regions where RHD is endemic (Hewitson et al., 2002; Hoosen et al., 2011; Mocumbi, 2012). Cardiac surgery is expensive, and a lack of infrastructure, human resources and equipment makes it almost impossible to provide timely and appropriate surgery. The collaboration between non-governmental agencies as well as humanitarian missions has been essential in providing a cardiac service in many parts of the developing world (Dearani et al., 2010).

In Africa, only isolated centres in South Africa, Egypt and Sudan offer significant training opportunities in cardiac surgery, and few centres consistently carry an independent annual surgical load of over 100 cases. Figure 1.4 indicates recent estimates of cardiac surgical centres in Africa (Zühlke et al., 2013).

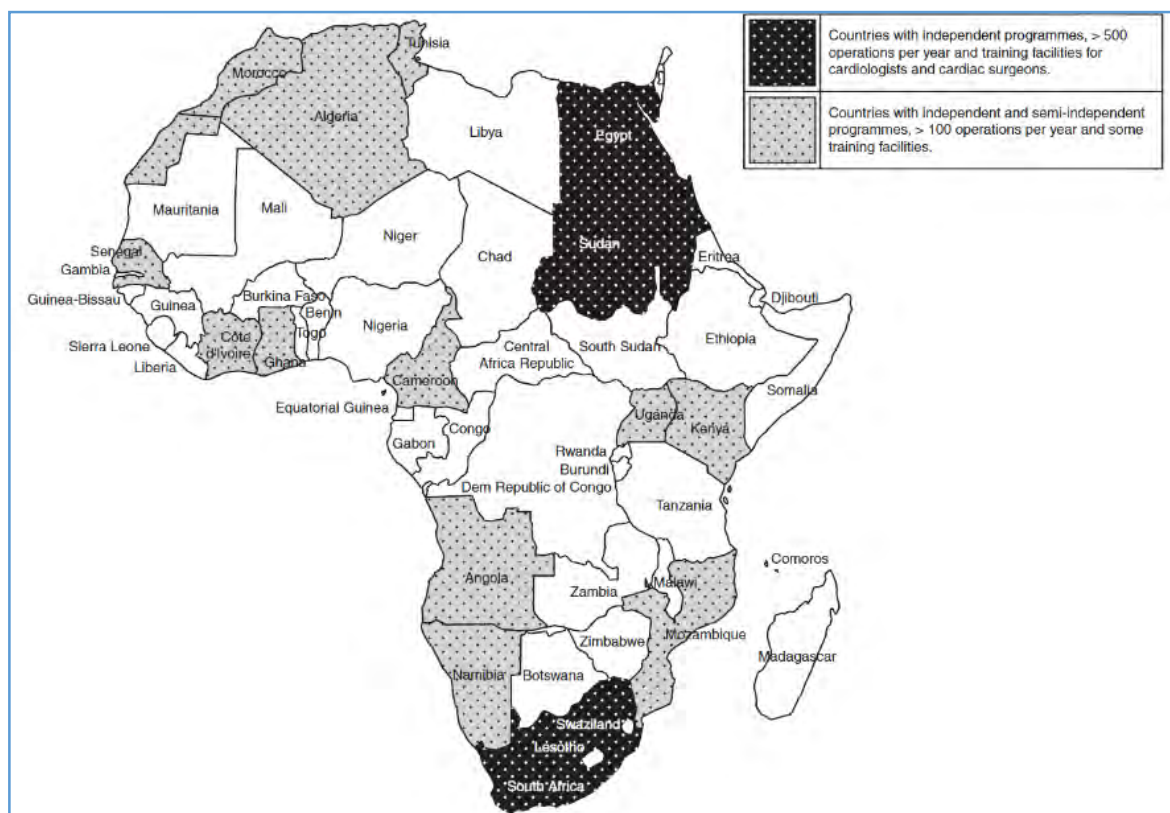


Figure 1.4. Countries with established cardiac surgery programmes (Zühlke et al., 2013)

Surgery for RHD is challenging, with the complication of prosthetic valves, anticoagulation and failed repairs being an ever-present issue. Results differ amongst units and relate largely to experience, the time of presentation, the timing of surgery and the presence of co-morbidities (Geldenhuys, 2011; Yankah et al., 2011). Countries with a high burden of RHD that are attempting to establish cardiac surgical programmes require comprehensive data regarding all aspects of cardiac surgery for RHD, including needs, costs, outcomes and complications .

#### **1.1.4 Defining the true burden of disease due to rheumatic fever and rheumatic heart disease**

Moving forward, it is critical to generate high-quality and comprehensive data regarding all aspects of the burden of ARF and RHD to inform national, regional and global control strategies (Carapetis and Zühlke, 2011). Comprehensive, prospective cohort studies of long-term outcomes, particularly related to the progression of disease and the distal sequelae of RHD, such as stroke, AF and IE, as well as the duration of disability, mortality rates and economic impact must be prioritised. These data will provide vital information to advocate for directed funding and public health interventions to control ARF and RHD.



## 1.2 The South African situation: Incidence, prevalence and complications of rheumatic heart disease in the current era

Although the global burden of estimates mentioned in the previous section included Africa, the data were scant with poor verification. This section focuses on South African data, with particular reference to the mortality and morbidity associated with RHD reported in local studies.

### 1.2.1 Incidence of acute rheumatic fever and rheumatic heart disease

A recent systematic review of the incidence of ARF clearly showed the dearth of high-quality data from sub-Saharan Africa, with no robust data from the region having been included in the study at all (Tibazarwa et al., 2008). This is illustrated in Figure 1.5 below (Tibazarwa et al., 2008).

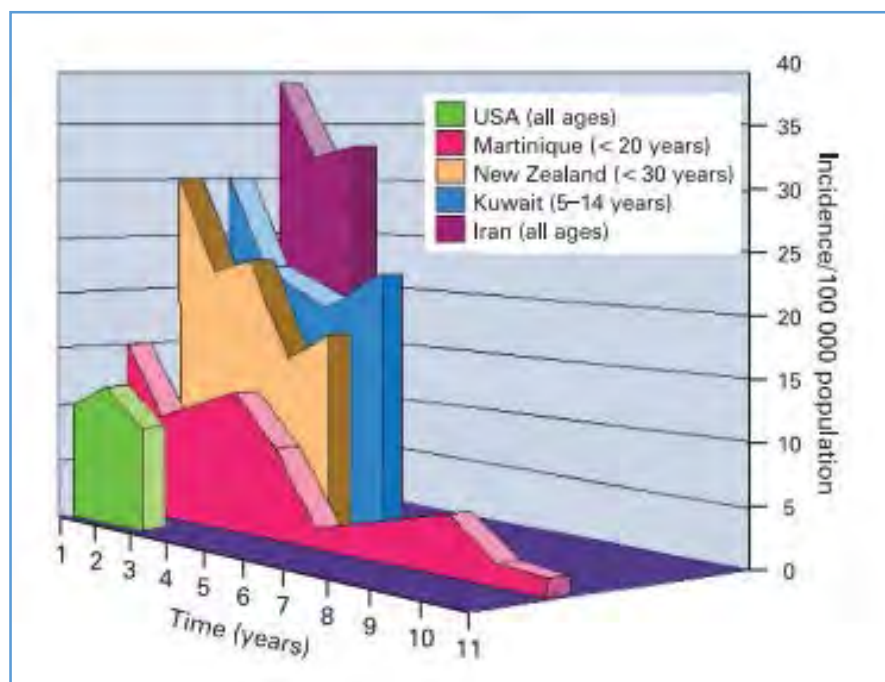


Figure 1.5. Annual specific incidence rate (temporal trend) of first attack of acute rheumatic fever (Tibazarwa et al., 2008)

That study also highlighted the problem in South Africa with regard to the poor quality of registry data, which had been previously described by Nkgudi et al. in a publication demonstrating the inadequacies of the local notification data (Nkgudi et al., 2006).

The Heart of Soweto study reported on the incidence and clinical characteristics of newly diagnosed RHD in adults from an urban African community, and found an estimated incidence of 23.5 cases/100,000 per annum (Sliwa et al., 2010). These patients were moderately to severely affected, with 17% having systolic dysfunction ( $EF < 45\%$ ), and a further 18% experiencing pulmonary hypertension, as evidenced by elevated right-sided pressure: 22% of this cohort required valve surgery within one year. A further 26% were admitted within 30 months for an initial diagnosis of suspected bacterial endocarditis. This study highlighted the severity of disease in patients presenting for the first time with symptomatic RHD, and emphasised the relevance of the ongoing complications of RHD.

### 1.2.2 Prevalence of rheumatic heart disease in South Africa

Previous reports cited sub-Saharan Africa as the region of the world with the greatest burden of RHD. A school screening study using auscultation conducted in Soweto in 1974 reported a prevalence of 6.9/1,000 in asymptomatic schoolchildren (McLaren et al., 1975). This had been preceded by a pilot study, which determined a prevalence of 5-10 per 1,000 (Pocock et al., 1968). A study from Hout Bay, Cape Town followed the same protocol as the McLaren study and reported the same prevalence of 6.9 per 1,000. Interestingly, though, half of the number of cases in which RHD had been detected had previously been diagnosed and were associated with poor adherence to secondary prophylaxis therapy (Bundred, 1986). This was followed by a study conducted in Inanda, Durban (Maharaj et al., 1987), whose results are summarised in Table 1.1 below. Calls for a national RHD control programme incorporating local registries followed, especially when surgical reviews published in the subsequent decade (the 1990s) reported significant morbidity and mortality associated with chronic RHD (Marcus et al., 1994; McLaren et al., 1994).

Table 1.1. Prevalence using clinical auscultation: South African studies

Reference	Town	Published	Population	N	Prevalence (per 1,000 population) [95% CI]
<b>Pocock et al. 1968</b>	Johannesburg	1968	2-12 yrs.	428	5-10
<b>McClaren et al. 1976</b>	Johannesburg	1976	2-18 yrs.	12,050	6.9 [5.27-82.6]
<b>Maharaj et al. 1979</b>	Durban	1979	4-18 yrs.	4,408	1.0 [16.8-26.2]
<b>Bundred et al. 1986</b>	Cape Town	1986	6-17 yrs.	1,150	6.9 [3.08-13.66]

Acronyms: N – number; CI – confidence interval

Since 1994, however, there have been significant advances in primary health care initiatives within the health care sector, and a renewed focus on improved health care delivery (Mayosi et al., 2012). South Africa has emerged as a leading economic force in the sub-Saharan region, having undergone major socio-political changes since the first free elections in 1994, and the transition to democratic leadership. Yet, extreme income disparities remain. South Africa has the dubious distinction of having the highest income inequality in the world, which is comparable only to Brazil and Chile (Leibbrandt et al., 2010). These disparities translate into continued high levels of diseases of poverty in the population, such as RHD and tuberculosis, resulting in significant morbidity and mortality (Barter et al., 2012). It is thus of interest to ascertain whether these efforts with regard to primary health care have translated into either a decreased RHD burden within the country or given rise to a transitional ARF/RHD epidemiology. Figure 1.6 below shows the effect of improved public health measures on valvular heart disease; such measures have included improved sanitation, better housing, reduced overcrowding and the widespread introduction of antibiotics. This has changed the epidemiology of ARF and RHD from a disease of young people to an aged population with existing disease and very few incident cases in developed countries.

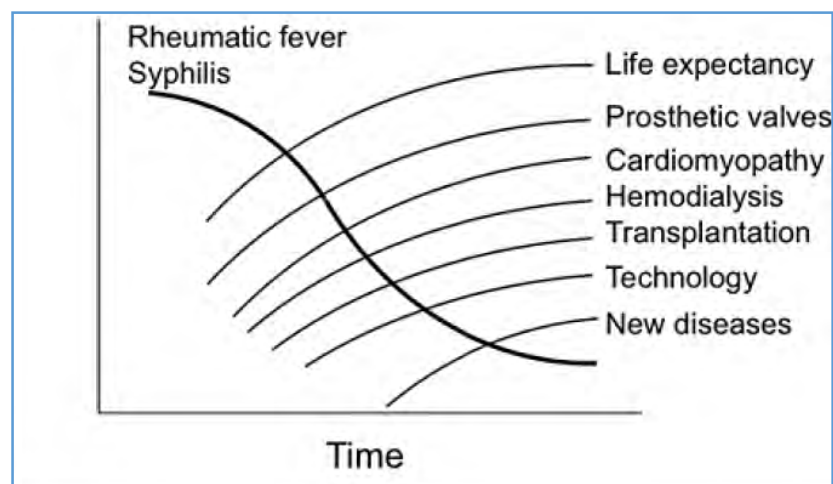


Figure 1.6. Factors affecting aetiology of valvular heart disease over the past half century (Boudoulas et al., 2013)

### 1.2.3 Outcomes of rheumatic heart disease in South Africa

Two African studies have recently determined that complications such as impaired systolic function, AF and right heart failure (RHF) were already present at first diagnosis of RHD (Sliwa et al., 2010). The Heart of Soweto study determined that patients were moderately to severely

affected, with 17% having systolic dysfunction (EF<45%) and 22% of the total cohort requiring valve surgery within one year (Sliwa et al., 2010).

A study from Uganda that reviewed the presenting features of newly diagnosed RHD patients reported that 46% presented with severe heart failure, while 54% had established pulmonary hypertension, 14% had AF and 8% had IE (Zhang et al., 2013). Hospital-based studies report that RHD accounts for 7-34.0% of cardiovascular disease-related hospital admissions or echocardiographic examinations performed in institutions across Africa (Sani et al., 2007a; Sani et al., 2007b; Soliman and Juma, 2008).

It has been estimated that up to 7.5% of all strokes occurring in less developed countries could be the direct result of RHD (Carapetis et al., 2005). In 2008 (Mayosi, 2007; Ntusi and Mayosi, 2009), RHD was found to be the second most significant contributor to cardiac failure in sub-Saharan Africa. The Randomised Evaluation of Long-Term Anticoagulation Therapy (RE-LY) Atrial Fibrillation (AF) registry determined that RHD was present in only 2.2% of North American patients with AF, in comparison with 21.5% in Africa and 31.5% in India (Oldgren et al., 2014). This demonstrates the contribution of RHD to the prevalence of AF in these countries. In the Heart of Soweto study, looking at AF, 21% of the subjects had RHD as a co-morbidity (Sliwa et al., 2010). Previous studies also established the role of RHD in IE, with RHD being the major predisposing factor in a prospective study from Cape Town. This study further demonstrated that the vast majority of affected patients (76.6%) had RHD, with a mortality rate of 35.6% (Koegelenberg et al., 2003).

These complications influence the quality of life of affected patients considerably, as well as reducing their education and employment possibilities, and thus posing a significant cost to the state. A contemporary review of the fatal and non-fatal outcomes of RHD using case-fatality rates and cause-specific mortality rates will allow for targeted interventions in areas of critical need. The studies contained within this thesis were designed to provide this information.

### **1.3 Natural history of asymptomatic rheumatic heart disease**

Sections 1.3 and 1.4 summarise relevant aspects of asymptomatic RHD, reviewing the current information regarding the natural history of asymptomatic RHD, screening for asymptomatic RHD and the use of standard and alternate screening modalities.

The first published paper on the natural history of rheumatic fever was published in 1868 by William Gull, reporting on the findings of 25 cases of ARF (Gull and Sutton, 1869). The natural history of progression to RHD has been well documented by classical texts from Bland and Duckett Jones, describing the natural history of ARF and RHD, and detailing the 20-year follow-up on 1,000 children from the House of the Good Samaritan in Boston, from 1921 onwards (Bland and Duckett Jones, 1951). Published in 1951, this report has remained the basis of much of our understanding regarding the progression of the disease since then. Uniformly, these early reports make several critical observations. Firstly, the association between tonsillitis/upper respiratory tract infection and subsequent rheumatic fever was documented (Figure 1.7) (Bland and Duckett Jones, 1951); secondly, the relationship between overcrowding, poor living conditions and subsequent infection was clearly shown; and thirdly, the consequences of the progression from ARF to RHD and the associated mortality rates were discussed.

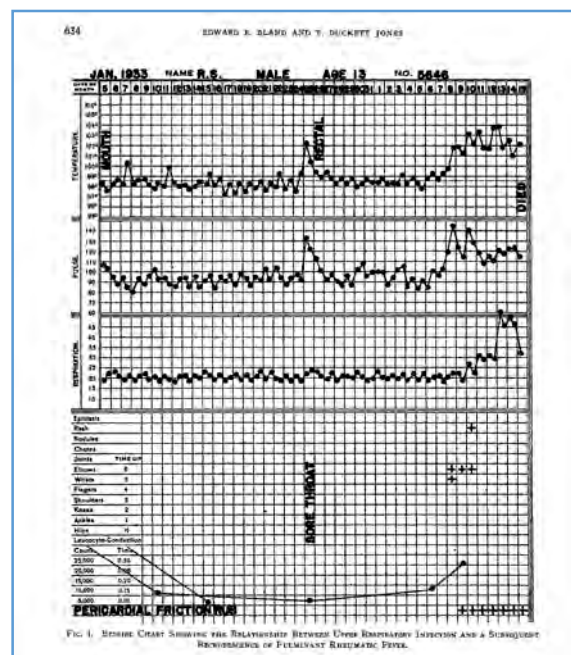


Figure 1.7. Clinical observations of the events preceding the appearance of rheumatic fever (Bland and Duckett Jones, 1951)

Over the past decades, studies have confirmed the key elements in the pathogenic cascade. The first of these is the causative agent, i.e., GAS, and the ubiquitous childhood infection, pharyngitis (Carapetis et al., 1996).

The second element is based on the fact that several key elements coalesce to increase the risk, with the highest risk among individuals who are exposed to socioeconomic deprivation (Brown et

al., 2007) and environmental factors (Steer et al., 2002), or who have the genetic predisposition for the disease (Engel, 2007). Finally, concerted efforts have been made to understand and clearly define the pathophysiological mechanisms that result in rheumatic fever and in the progression to RHD, and to conduct the all-important search for a vaccine (Azevedo et al., 2012; Guilherme et al., 2004; Guilherme et al., 2009; Guilherme et al., 2011). Figure 1.8 illustrates these elements and the potential points of intervention.

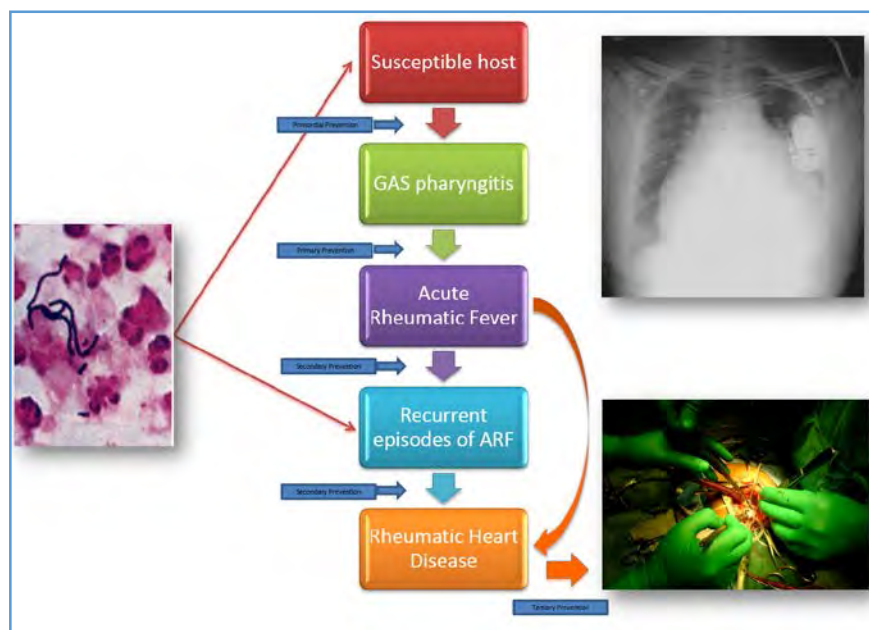


Figure 1.8. The causal pathway to rheumatic heart disease and points of intervention

### 1.3.1 Natural history of subclinical carditis in acute rheumatic fever

Subclinical carditis (manifesting in echocardiographic lesions in the absence of a murmur) in the context of ARF is associated with either persistence or regression of disease, in follow-up studies. The Doppler echocardiographic features of subclinical rheumatic carditis were characterised by Minich (Minich et al., 1997), while Figueroa and others were the first to report on the natural history of subclinical carditis in patients with ARF (Figueroa et al., 2001). The long-term follow-up of subclinical carditis associated with ARF has determined that valve lesions persist in 30% of patients after five years (Karaaslan et al., 2003; Lanna et al., 2003; Ozkutlu et al., 2003).

A systematic review of studies of subclinical carditis also showed that approximately half of the patients diagnosed with subclinical carditis at the time of ARF showed persistence or deterioration of their carditis in the following two years (Tubridy-Clark and Carapetis, 2007). As a result, stricter echocardiographic criteria were proposed, using both qualitative and quantitative elements, in an effort to identify those patients who are likely to have significant irreversible damage of the heart valves (Caldas et al., 2007; Vijayalakshmi et al., 2008; Wilson, 2008).

### 1.3.2 Progression of echocardiographic changes detected as part of auscultation-based screening

These echocardiographic follow-up studies in the context of ARF showed similar results to the clinical studies that had been conducted before echocardiographs came into use.

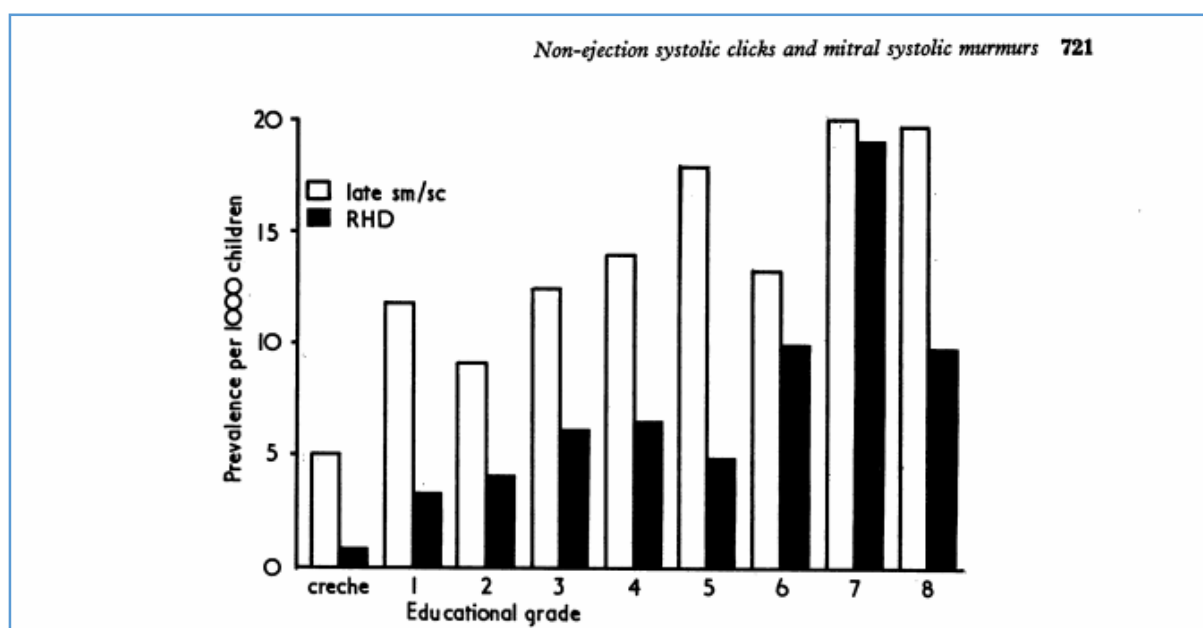


Figure 1.9. Prevalence of non-ejection clicks and mitral systolic murmurs (Cohen et al., 1978)

In a four-year follow-up study of patients with abnormalities detected on auscultation (Figure 1.9) (McLaren et al., 1975), patients with short systolic murmurs and non-ejection clicks (most likely corresponding to borderline disease, using today's definitions) were most likely to improve, with very few progressing to overt RHD (Cohen et al., 1978). In comparison, patients with bona fide murmurs were found to have persistent clinical findings, with a small percentage requiring tertiary follow-up or intervention (Figure 1.10) (Cohen et al., 1978).



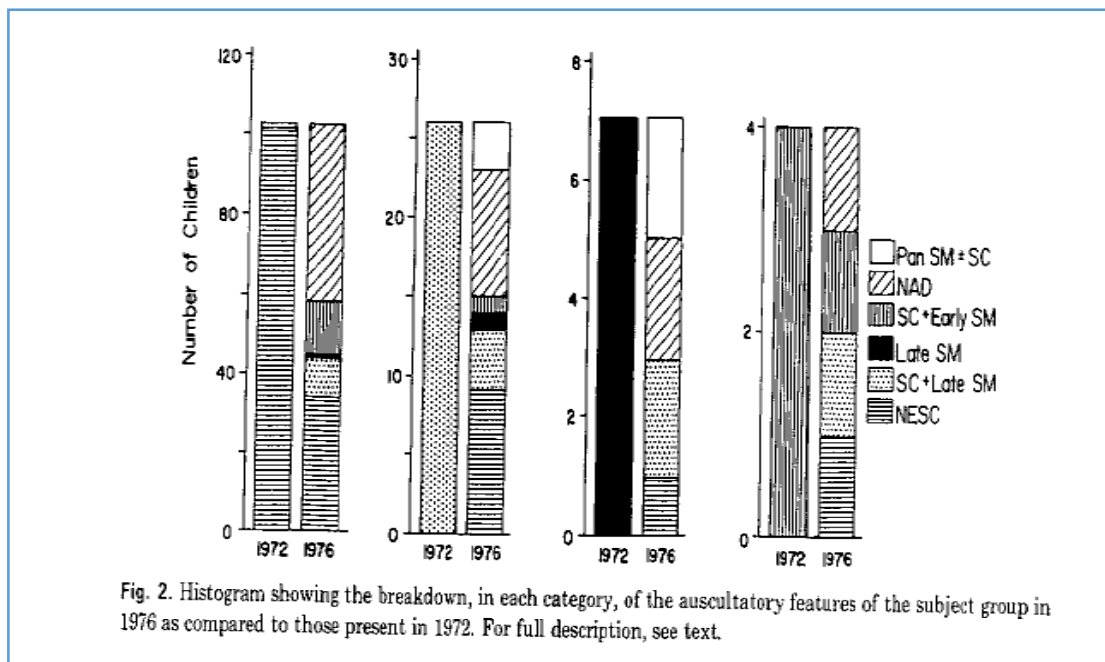


Figure 1.10. Features relating to auscultation of the 1976 group compared with those in 1972 (Cohen et al., 1978)

### 1.3.3 Screening using portable echocardiography

The first echo-based prevalence study was performed in 1996 in two rural schools in Kenya, located in Kapyemit and Kipkenko respectively (Anabwani and Bonhoeffer, 1996). There were several novel aspects to this study: Firstly, it was the first study to use portable echocardiography as the primary modality to assess the prevalence of RHD and congenital heart disease and to characterise trivial valvular regurgitation. Secondly, a generator powered the echo machine in consideration of the extremely rural setting. Finally, the study proposed following the evolution of trivial mitral and aortic regurgitation (AR) by using a randomised stratified sample of secondary prophylaxis. The latter aspect of the study has not subsequently been reported upon; however, the potential benefit of a randomised controlled trial of secondary prophylaxis in children with subclinical carditis has been suggested, although such a study would face substantial logistical and ethical hurdles (Ba-Saddik et al., 2011). This study went under-recognised for some time, during which several clinical auscultation screening studies were conducted (Sudeep and Sredhar, 2013) until a report was published a decade later. Marijon et al. focused attention on what could be referred to as a partly submerged iceberg of asymptomatic RHD: they found that the number of cases detected by echocardiography, which is the recognised standard for assessing valvular



morphology and function, differed by a factor of up to 10 times from cases detected by means of auscultation (Marijon et al., 2007).

The use of portable echocardiography to screen asymptomatic children and young adults for RHD in countries where this disease is endemic has shown that the disease may in fact be affecting 62 million to 78 million individuals worldwide. This could potentially result in 1.4 million deaths per year from RHD and its complications (Paar et al., 2010). The majority of these people are moreover living in countries with limited access to cardiac surgery (Jackson et al., 2011; Mocumbi, 2012). Thus, the prospect of being able to detect the earliest changes of RHD in high-prevalence populations, followed by the implementation of secondary prophylaxis to retard progress to overt disease, has been met with great enthusiasm. This has resulted in a dramatic increase in the number of echocardiographic screening studies for RHD over the past 15 years in Africa, South Asia, the Middle East, South America and Australasia. Figure 1.11 summarises the results of studies conducted in Africa in the past 10 years (Zühlke et al., 2013).

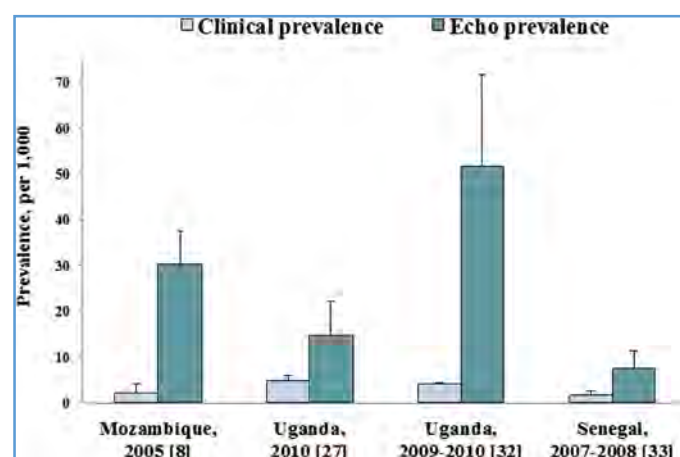


Figure 1.11. RHD detected amongst schoolchildren by means of echo-based screening in Africa (Zühlke et al., 2013)

These studies have focused on Africa, India, the Middle East, Nicaragua and the Pacific Islands, which have all traditionally been hotspots of the disease. They have not only revealed a large burden of subclinical disease, but have also demonstrated the superiority of echocardiography over auscultation in detecting early rheumatic structural and functional changes of the mitral and aortic valves (Cramp et al., 2012; Marijon et al., 2008; Webb et al., 2011). Screening for asymptomatic RHD has given rise to much debate, including around the validity of the findings (Marijon et al., 2007), the criteria chosen to define RHD, and the impact of important public health issues (Marijon et al., 2009; Zühlke, 2009). These debates relate to the ability of developing countries to

manage the large numbers of patients who will be detected by means of echocardiography, the appropriate treatment for these patients and the cost-effectiveness of screening for RHD. Currently, screening is underway in virtually all regions of the world where the disease is prevalent, and an urgent call has gone out for further and extensive research in this area, to answer some of these questions (Carapetis and Zühlke, 2011).

The publication of the WHF criteria for the diagnosis of subclinical RHD consolidated international consensus and opinion in developing and proposing a set of evidenced-based guidelines for the echocardiographic screening of RHD in asymptomatic populations (Remenyi et al., 2012a) (see Table 1.2). This represents an important new contribution to the research landscape of RHD. It makes it possible to compare different populations and ultimately to pool data, conduct systematic reviews and engage in meta-analyses. In addition, these guidelines provide a much-needed objective method to follow children with subclinical carditis detected in the current round of screening studies, to determine the progression of RHD and the recurrence rates of ARF. The importance of a unified set of criteria is demonstrated in Figure 1.12, which expresses the variability of the prevalence of RHD among 2,170 Mozambican schoolchildren, using auscultation and four different echocardiographic criteria (Zühlke and Mayosi, 2013).

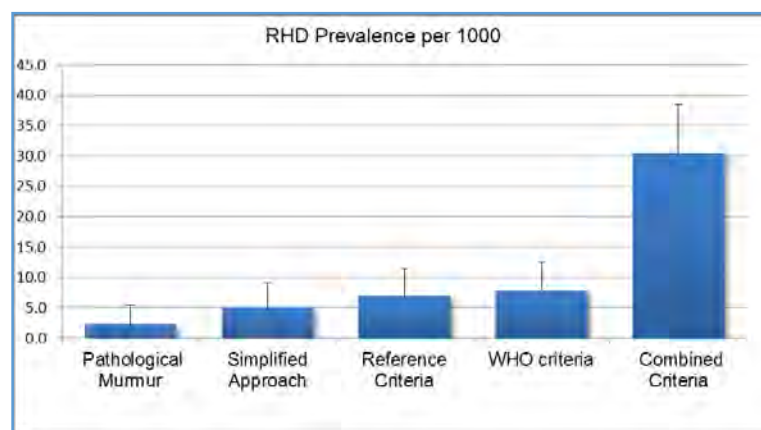


Figure 1.12. Comparison of rheumatic heart disease prevalence, utilizing different criteria for the same dataset (Zühlke and Mayosi, 2013)

Table 1.2. World Heart Federation criteria for echocardiographic diagnosis of rheumatic heart disease

2012 World Heart Federation criteria for echocardiographic diagnosis of rheumatic heart disease *	
<b>Echocardiographic criteria for individuals aged ≤20 years</b>	
<b>Definite RHD (either A, B, C, or D):</b>	
A) Pathological MR and at least two morphological features of RHD of the MV	
B) MS mean gradient ≥4 mmHg	
C) Pathological AR and at least two morphological features of RHD of the AV‡	
D) Borderline disease of both the AV and MV	
<b>Borderline RHD (either A, B, or C):</b>	
A) At least two morphological features of RHD of the MV without pathological MR or MS	
B) Pathological MR	
C) Pathological AR	
<b>Criteria for pathological regurgitation</b>	
<b>Pathological mitral regurgitation</b>	<b>Pathological aortic regurgitation</b>
(All four Doppler echocardiographic criteria must be met)	
Seen in two views	Seen in two views
In at least one view, jet length ≥2 cm	In at least one view, jet length ≥1
Velocity ≥3 m/s for one complete envelope	Velocity ≥3 m/s in early diastole
Pan-systolic jet in at least one envelope	Pan-diastolic jet in at least one
<b>Morphological features of RHD</b>	<b>Morphological features of RHD</b>
<b>Features in the MV</b>	<b>Features in the AV</b>
AMVL thickening ≥3 mm (age-specific)	Irregular or focal thickening
Chordal thickening	Coaptation defect
Restricted leaflet motion§	Restricted leaflet motion
Excessive leaflet tip motion during systole	Prolapse
* Adapted from Remenyi et al., 2012). See full article for important explanatory notes and caveats.	
Acronyms: AMVL – Anterior mitral valve leaflet; AR – aortic regurgitation; AV – aortic valve; MR – mitral regurgitation; MV – mitral valve; RHD – Rheumatic heart	

### 1.3.4 Progression of echocardiographic changes detected as part of screening

The natural history of subclinical RHD in asymptomatic populations without a previous history of ARF is not well characterised. Four studies have reported on the short-term progress of subclinical RHD detected by echocardiography (Bhaya et al., 2010; Bhaya et al., 2011; Paar et al., 2010; Saxena et al., 2011). Bhaya et al. showed that, within two years of follow-up, isolated mitral regurgitation or isolated valve deformities were likely to resolve in the absence of additional findings. In contrast, mitral regurgitation coexisting with valve deformities was more likely to persist (Bhaya et al., 2011). This implies that disease that has been classified as ‘definite’ by echocardiography (i.e., involving morphological and functional changes) is more likely to persist than disease that falls into the ‘borderline’ or ‘possible’ categories (i.e., with either morphological or functional changes). In follow-up investigations on 100 children over 3 to 27 months in the Rheumatic Heart Echocardiograms Utilisation and Monitoring Actuarial Trends in Indian Children (RHEUMATIC) study, the severity of subclinical RHD was found to be non-progressive in 68% of children, while the changes worsened in 4% and improved in 28% of children (Saxena et al., 2011). A similar pattern was reflected in the follow-up of participants in the probable and possible categories in Nicaragua (Paar et al., 2010). In these categories, 69% persisted and 9% worsened, while 32% of cases completely resolved.

The most recent review from Uganda confirms a similar pattern, with over half of the lesions unchanged, only one child presenting with clinical disease, and 91% of children screened being clinically well after 25 months of follow-up (Beaton et al., 2014b). This paper makes two additional important points: Firstly, it identifies additional risk factors for disease progression or persistence, viz. younger age ( $P=0.005$ ), higher anti-streptolysin O titres at diagnosis ( $P=0.005$ ) – and more morphological valve abnormalities ( $P=0.001$ ). Secondly, it notes two episodes of ARF in its cohort, neither of which had a history of sore throat. One of these was on regular four-weekly benzathine penicillin, yet progressed to clinical disease with cardiac failure, while the second, who had not been on benzathine, commenced such antibiotic treatment after the ARF episode. Together, these studies (Table 1.3) indicate that early forms of suspected RHD, detected by either auscultation or echocardiography, in asymptomatic populations may be associated with the resolution or disappearance of changes in 30-40% of subjects.

Table 1.3. Short-term follow-up studies: Study characteristics and outcomes

Study characteristics	Bhaya et al Nicaragua	Saxena et al Harayana, India	Bhaya et al Bikaner, India	Beaton et al Uganda
<b>Number of school children screened</b>	3,150	6,270	1,059	4,869
<b>Diagnostic criteria</b>	NIH	WHO criteria	WHO criteria	WHO* WHF*
<b>Number (%) with subclinical RHD</b>	137 (4.3)	128 (2.0)	54 (5.1)	72 (1.5)
<b>Number (%) of cases followed-up</b>	126 (92.0)	100 (78.1)	54 (100)	51 (82)
<b>Secondary prophylaxis</b>	Yes	No	Yes	Yes*
<b>Follow-up duration (months)</b>	4-1	3-27	24	7-25
<b>Median and/or mean</b>	Median 5.7	Mean 15.4	NR	Median 25
<b>Subclinical lesion unchanged</b>	73 (57.9)	68 (68)	36 (66.7)	27 (52.9)
<b>Subclinical lesion improved or resolved</b>	41 (32.5)	28 (28)	18 (33.3)	20 (39.3)
<b>Subclinical lesion worsened</b>	12 (9.5)	4 (4)	0 (0)	4 (7.8)
<b>Clinical episodes of ARF during follow-up</b>	NR	0	0	2
<b>Overt/Severe disease</b>	NR			1
<b>Additional risk factors identified</b>				Yes*

\*See text for detailed account. Acronyms: NIH – National institutes of Health; NR – not reported; WHF – World Heart Federation; WHO – World Health Organisation.

There are several problems with the limited number of studies of the natural history of latent RHD detected by screening echocardiography (Beaton et al., 2014b; Bhaya et al., 2011; Paar et al., 2010; Saxena et al., 2011). Firstly, these studies have had relatively short follow-up periods ranging from 6 months to 2 years. The natural history of latent RHD beyond this period is unknown. Secondly, non-standardised criteria for the diagnosis of RHD have been used in three of the four studies of this question to date (Bhaya et al., 2011; Paar et al., 2010; Saxena et al., 2011), which are associated with widely varying estimates of the prevalence of the disease even in the same study (Zühlke and Mayosi, 2013). Finally, these studies have had variable use of penicillin prophylaxis in patients with latent RHD, which may affect the natural history of the condition.

The importance of the WHF criteria is re-emphasised by these publications, and thus, these criteria should be used to assess the natural history of latent RHD disease in schoolchildren beyond two years. This is needed to address the questions regarding the natural history of subclinical lesions detected upon screening.

## **1.4 Alternate modalities for screening for asymptomatic rheumatic heart disease**

The approach used for detecting RHD in screening studies of asymptomatic children has changed progressively over the past two decades, moving away from auscultation to different portable echocardiography protocols. Although the cost of portable echocardiogram machines is appreciably less than that of conventional machines, they are nevertheless still prohibitively expensive for those developing countries where RHD is endemic. The WHF criteria require the acquisition of multiple images by a skilled technician, the use of an echocardiogram machine with Doppler capability and the interpretation of images by an experienced reviewer (Remenyi et al., 2012a; Saxena et al., 2013). However, echocardiography machines with Doppler capability remain expensive, and this, together with the need for highly trained personnel to perform these echocardiograms, renders them less affordable in many low-resource settings (Zühlke and Mayosi, 2013).

### **1.4.1 Alternate protocols for screening using echocardiography**

Several key papers have addressed the problem of high costs, of both equipment and health personnel expertise, and the complicated protocols used to screen for and confirm the disease (Table 1.4). Reeves et al. were the first to report on the use of a low-cost portable machine, a non-expert operator and an abbreviated echocardiography screening protocol, in Fiji (Reeves et al., 2011). They found that, with echocardiography averaging less than four minutes per participant, a comprehensive screening programme could cost less than US\$40 per case detected. This study supported the use of non-expert operators as screening personnel with only screen-positive participants requiring review and confirmation by specialists. A subsequent report from Fiji has, moreover, demonstrated the accuracy of nurse-led echocardiography screening, following an intensive period of training and supervised field-testing (Colquhoun et al., 2013).

Table 1.4. Alternate methods of screening for rheumatic heart disease

Screening method	Reference	Sample Size	Time taken to complete echo	Reviewer */operator#	Criteria	Sensitivity and/or specificity
<b>Screening using abbreviated protocol echocardiography. protocols</b>	Marijon et al.	3,677	not known	paediatric cardiologist*#	Abbreviated protocol§	
	Reeves et al.	362	5 minutes	paediatrician*/registrar#	WHO/NIH 2005	
	Beaton et al.	4,869	2 minutes	paediatric cardiologist*#	WHO/NIH 2005	
<b>Screening using non-cardiologist reviewers</b>	Reeves et al.	362	as above	paediatrician*/registrar#	WHO/NIH 2005	
<b>Pilot studies</b>						
<b>Nursing reviewers</b>	Colquhoun et al.	50	not known	nurse*#	mitral regurgitant jet>1.5cm§	Sensitivity: 100%, 83% Specificity: 67.4%, 79%
<b>Hand-held echocardiography</b>	Beaton et al.	125	not known	paediatric cardiologist*#	modified WHF criteria§	Sensitivity: 90.2% Specificity: 92.9%

§ Defined in article. Acronyms: NIH – National Institutes of Health; WHF – World Heart Federation; WHO – World Health Organisation.

In 2012, Mirabel et al. evaluated a simplified echocardiography protocol and reviewed the Mozambique screening data, comparing the simplified approach to a set of reference criteria (Mirabel et al., 2012b). The authors subsequently proposed a simplified protocol – the single mitral regurgitation jet-length criterion, which performed as well as the reference criteria did. A two-stage protocol, conducted in Uganda (Beaton et al., 2012), focused only on the left-sided valves in the initial echocardiogram, which was followed by a comprehensive confirmatory echocardiogram among patients with abnormal findings. The Ugandan protocol resulted in an initial screening time of only two minutes, which meant that a single echocardiographer could screen 200-250 children on a single day, thus enabling 4,869 children to be screened within four months.

Previous studies of RHD that has been detected by means of a screening echocardiogram have determined that nearly all cases of RHD (>97%) involved primarily the mitral valve, with a minority involving both the mitral and aortic valves. Rare cases of isolated aortic valve disease have occurred, with no isolated history of tricuspid or pulmonary disease (Roberts et al., 2013a). In addition, no study using first-line echocardiography has detected any stenotic lesions; these were only detected using auscultation followed by echocardiography (Sadiq et al., 2009). A protocol focusing on the mitral valve alone is therefore worthy of consideration.

The consideration of alternate modalities and methods for screening, in particular in rural and low-resource settings, is important before researchers recommend large-scale screening.

#### **1.4.2 Computer-assisted auscultation**

Cardiac auscultation is an indispensable diagnostic aid that allows experienced clinicians to diagnose cardiac disease consistently and accurately (Woywodt, 1999). However, cardiac auscultation is inherently qualitative, highly subjective and requires considerable skill and experience (Hanna and Silverman, 2002). Moreover, recent reports have documented poor accuracy in discerning an innocent murmur from one suggestive of pathology (Vukanovic-Criley, 2006). Since the first screening study comparing auscultation with echocardiography was published, the number of cases detected by echocardiography compared with auscultation have differed by a factor of up to 10 times, seemingly confirming the poor sensitivity of auscultation (see Figure 1.13) (Marijon et al., 2012). However, there have not been any studies to date utilising an objective automated auscultation decision in this environment.



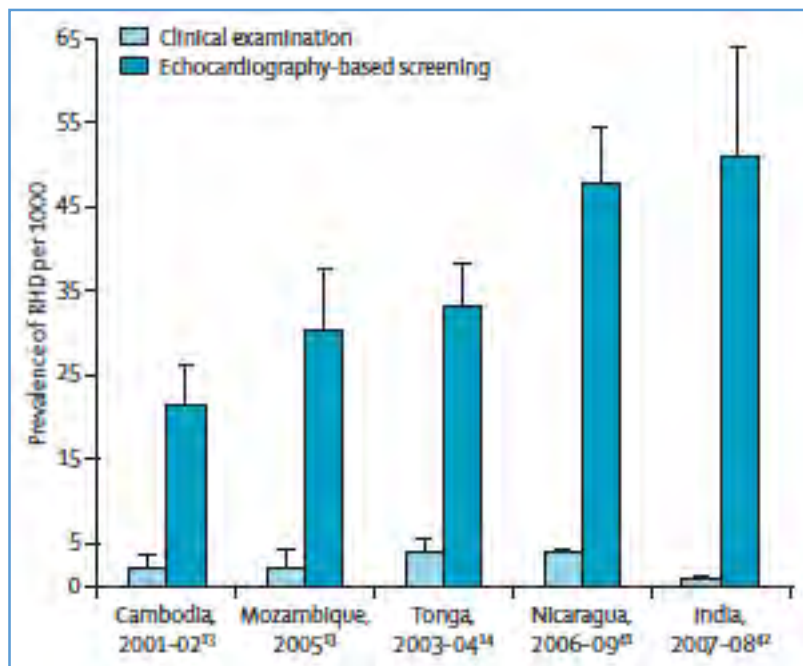


Figure 1.13. Screening using auscultation versus echocardiography (Marijon et al., 2012)

Computer-assisted auscultation (CAA) has been suggested as a diagnostic aid in clinical practice, to identify pathological murmurs and act as a referral decision support tool, particularly in resource-limited settings (Botha et al., 2010). Although electronic stethoscopes have been available commercially for some time, it is only in the past decade that the associated computer analysis has made rapid advances (Tavel, 2006, 2010). The electronic stethoscope produced by Zargis® Medical Corporation was the first product with clinically validated indications – including for the detection of heart murmurs – for use by physicians. Primary care physicians were thus able to decrease their average false positive referral rate from 37% to 21% ( $P < 0.001$ ), while reducing their false negative rates from 13% to 7% (Watrous et al., 2008). Diacoustic® recently published findings of their decision support system, which targets the paediatric population. A specificity of 94% and a sensitivity of 91% were achieved using novel signal processing techniques and an ensemble of neural networks as classifiers (Fourie, 2009; Pretorius et al., 2010).

CAA is now able to conduct a spectral and temporal analysis of heart sounds and to classify heart sounds and murmurs into normal and abnormal, using neural network pathways (Noponen et al., 2007). CAA adds increased objectivity to a traditionally subjective, increasingly difficult clinical skill. A diagnostic support tool that could increase the sensitivity and specificity of echocardiography referral decisions could potentially be highly cost-effective, facilitate a more efficient use of personnel and resources, and may indeed be the promising technology required to

improve the referral decisions of primary care physicians. This technology moreover promises to have value in teaching auscultation as well as in screening for structural heart disease (Zühlke et al., 2012a).

### **1.4.3 Hand-held echocardiography**

The advent of hand-held echocardiogram machines ushers in a new possibility for their use in screening programmes, among other point-of-care services. Although the medical community has embraced the more affordable ultra-portable hand-held echocardiogram machine since its inception, the WHF criteria for diagnosing definite and borderline disease in subclinical populations require an accurate assessment of Doppler gradients, which these machines cannot currently provide. In fact, the WHF guidelines refer specifically to the technical limitations of hand-held echocardiography, in particular relating to its lack of Doppler capabilities, and emphasise that hand-held echocardiography is unable to acquire all the measurements required for the application of the WHF criteria.

The most recent report from Uganda compared hand-held ultra-portable echocardiography that lacked an associated Doppler capability with standard portable echocardiography. They demonstrated reasonable sensitivity and specificity for the early detection of RHD when the authors' modified WHF criteria, used with hand-held ultra-portable echocardiography, were compared with the published WHF criteria, which are used with standard portable echocardiography (Beaton et al., 2014a).

Thus, it remains uncertain which is the most feasible and appropriate echocardiographic protocol for undertaking RHD screening in resource-poor settings (Carapetis and Zühlke, 2011). Nonetheless, given the high burden of symptomatic disease (Zühlke et al., 2013), those living in low-income countries do require simple, affordable and reliable approaches to large-scale RHD screening, and thus one of the aims of this thesis is to ascertain such an approach.

## 1.5 Baseline characteristics of symptomatic disease

This final section in my introduction explores the current literature on clinical characterisation of symptomatic RHD, and summarises key information on mortality and morbidity estimates.

There have been few descriptions of the clinical characterisation of cases on RHD registers and of the incident cases presenting at hospitals from low- and middle-income countries. Several papers have reviewed the predominance of women over men in smaller studies. Speculation and some research have focused on the contribution of genetics and differing health-seeking behaviours to the increased ascertainment of RHD during pregnancy, resulting in more women in most studies compared with men (Okello et al., 2013; Sliwa et al., 2010; Zhang et al., 2013). Of paramount concern, however, are the consequences for women with RHD who are pregnant or going through labour; RHD contributes to significant maternal mortality in low-resource settings. A recent review of all screening studies from low- and middle-income countries showed a female predominance in virtually all studies (see Figure 1.14) (Sudeep and Sredhar, 2013).

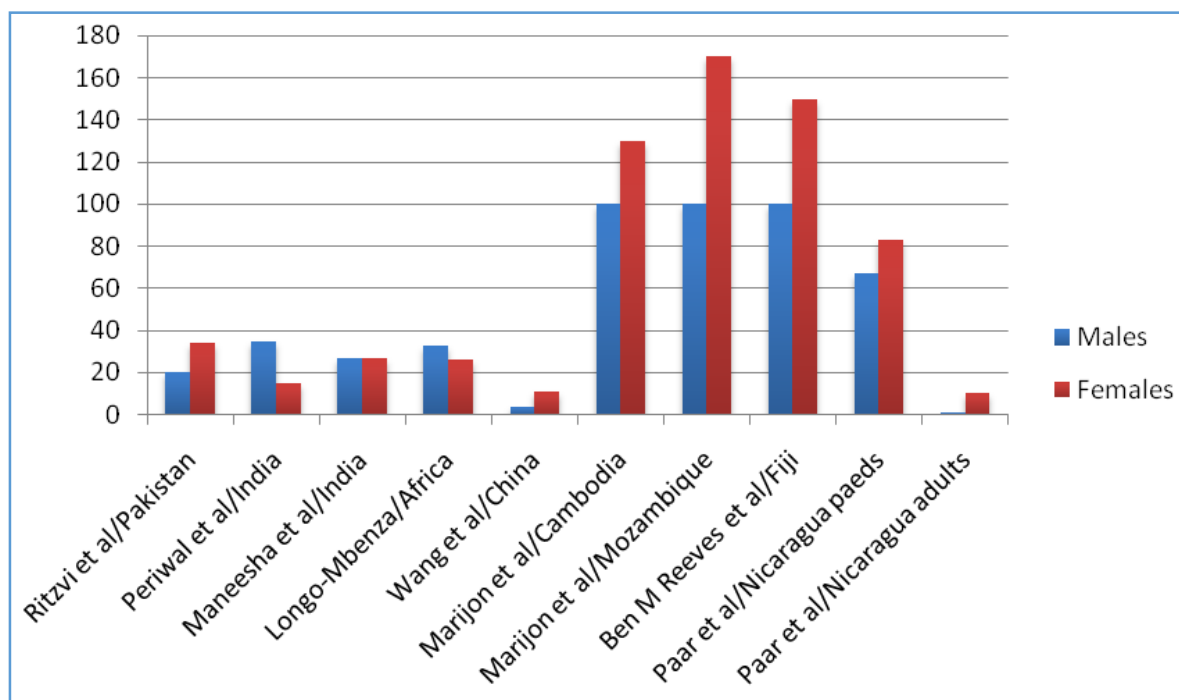


Figure 1.14. Prevalence of rheumatic heart disease by gender (Sudeep and Sredhar, 2013)

The accelerated course of mitral stenosis among children in Africa and India has been well described in retrospective reviews (Tadele et al., 2013). Pure mitral stenosis has even been reported in children younger than five years of age (Betigeri et al., 2013). Advanced manifestations of valve disease indicate the level of complexity and severity of hospital-based RHD. Other reviews in the recent past have highlighted a similar severity at presentation (Clur, 2006; Essop and Nkomo, 2005; Tantchou Tchoumi and Butera, 2009). These reports and others (Sani et al., 2007a; Sani et al., 2007b; Tantchou Tchoumi and Butera, 2009) have promoted renewed efforts to ascertain the natural history of the disease, to focus on systematic prospective high-quality data associated with detailed echocardiography studies, and to plan future interventions (Zühlke et al., 2012b).

Secondary prevention using penicillin prophylaxis administered through register-based programmes has long been thought to be the most efficient and cost-effective form of intervention (McDonald et al., 2005). Despite recent debates (Seckeler et al., 2010; Steer et al., 2011; Watkins and Mayosi, 2011), secondary prophylaxis is an established practice and forms part of all the current published guidelines (Atatoa-Carr et al., 2008; Department of Health, 2003; RHD Australia (ARF/RHD writing group) National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand, 2012; Saxena et al., 2008; WHO, 2004). Little is known about the adherence to oral and benzathine penicillin across income categories, nor about the use of interventions, such as oral anticoagulation, rates of surgery and valvuloplasty across country income categories.

### **1.5.1 Clinical characteristics in the context of a global transition**

The clinical characteristics of RHD in developing countries have unique disease patterns and presentations. Geographical differences among the characteristics of affected patients may demonstrate clinical significance if systematically documented, while there are few reports of the impact of country income categories on RHD.

The past decade has seen significant changes in the world economy, with the pace of per capita income growth in emerging and developing economies accelerating in a sustainable manner, substantially above that in advanced economies (Milanovic, 2012). This, together with the demographic transition in the developing world, viz. of slower population growth, has resulted in some health gains in impoverished communities, but it has also been associated with increasing inequality between higher- and lower-income groups. In 2008-2009, it was estimated that countries

in Africa had the highest income inequality metrics, with South Africa having the world's highest Gini coefficient, at 0.7 (The world development report online, 2014). Developing and emerging economies in Africa, the Middle East and India are also categorised as being in the lower quartiles of human development, according to a composite statistic of life expectancy, education and income indices (United Nations Development Programme, 2013). In comparisons between income categories, the risk-factor burden for cardiovascular disease was lowest in low-income countries, but the rates of major cardiovascular disease and death were substantially higher in such countries (Yusuf et al., 2014). The lower rate of disease and death in high-income countries may be due to better control of risk factors and more frequent use of proven pharmacological and revascularisation interventions. The effect – in the economic position of emerging economies – of these indices and transitions on countries in these regions most affected by RHD is unclear.

## **1.6 Sequelae of rheumatic heart disease**

Developing countries face an indisputable burden when established RHD cases present with significant complications. *De novo* cases of established RHD made up almost 10% of the burden at a tertiary cardiac centre in Soweto, South Africa (Sliwa et al., 2010), while complications relating to RHD, such as stroke, IE and heart failure (Kolo et al., 2010) are also strongly evident in clinical practise. In Nigeria, the most common sequelae among hospital-based RHD patients were pulmonary hypertension, CHF, and IE (Akinwusi et al., 2013).

A recent study conducted at a university hospital in Dakar, Senegal – a review of cardiac disease in pregnancy – determined that 92% of women hospitalised because of heart disease during pregnancy, presented with RHD (Diao et al., 2011). Rheumatic mitral stenosis was by far the most frequent cause of heart disease during pregnancy, accounting for 64% of all cases. Of importance was the reported maternal mortality of 34%, while the mortality rate in the group with severe mitral stenosis was just under 50% (Diao et al., 2011). IE is also a known complication of RHD, both due to the damaged valves and the prothrombotic state of the RHD patient. In Turkey, a review showed that 36% of patients presenting with native and prosthetic valve endocarditis had RHD (Sucu et al., 2010). In recent reviews (Mayosi, 2007; Ntusi and Mayosi, 2009), RHD was the second most significant contributor to cardiac failure in sub-Saharan Africa. In the absence of newer, more effective drugs, better access to surgery, improved myocardial protective strategies, and the advanced health resources of the developed world, cardiac failure – in the developing world – is associated with a vastly different outcome (Mayosi, 2007). A case-fatality rate of 24% in a review

of childhood heart failure among the study population demonstrates the poor outlook for children with heart failure in the developing world. Poor prognostic indices that have been identified included the presence of underlying RHD (Omokhodion and Lagunju, 2005).

RHD is a significant contributor to strokes in the young and more generally among people living in developing countries. Strokes attributable to RHD have been associated with a twofold increased risk of death and an increased risk of recurrence (Wang et al., 2012a). A recent systematic review in Asia reported that the proportion of RHD in patients with stroke ranged from 3.5% to 23.2% (Wang et al., 2013). The mechanism for strokes in RHD is complex and is associated with the prothrombotic tendencies of RHD, the presence of left-atrial thrombus secondary to a dilated left atrium, or decreased systolic function and AF in patients with mitral stenosis (Carabello, 2005).

Mortality rates calculated from reported case fatality ratios in recent published reports reveal that the highest estimated mortality from RHD exists in Pakistan (3.7 per 100,000), while Mauritius has the highest mortality rates from ARF (4.32 per 100,000) (Jackson et al., 2011). This review used vital registration data to obtain mortality rates, and noted that these data were largely not available in Africa, thus resulting in a possible underestimation of the mortality rates for most of Africa. Gunther stressed this point in a letter to the *Lancet* in 2006: He pointed out that, in a rural Ethiopian community (Gunther et al., 2006), the annual mortality rate of patients with RHD was 12.5%, 10 times that of the mortality rate used by Carapetis and colleagues to estimate the worldwide annual mortality from RHD in 2005 (Carapetis et al., 2005).

It is clear that contemporary robust estimates of mortality and morbidity as well as rates of complications are urgently needed from the highest-prevalence areas, in order to have a more accurate assessment of the true disease burden.

## **1.7 Summary and rationale for this thesis**

For a long time, South Africa was thought to be the hotspot of ARF/RHD in Africa, south of the Sahara. However, the past two decades have seen tremendous changes in the country's socio-political climate with resultant changes and advances in healthcare. It is thus a good opportunity to conduct a robust systematic review to assess the contemporary burden of disease – incidence, prevalence and outcomes – to inform health planning and suggest future health policies around ARF/RHD in South Africa.

The use of screening echocardiography to diagnose asymptomatic RHD has led to reports showing an increased prevalence in all areas of the world besides Europe. However, there is evidence that, in many cases, the latent lesion is benign and normalises in at least 30-40% of individuals. To date, however, no long-term studies beyond 27 months have been undertaken. Until a larger registry can report large-scale and long-term findings, there is a clear need for longer-term follow-up studies to evaluate the natural history of echocardiographically detected RHD.

Portable echocardiography is a promising screening test with a high sensitivity for the detection of early forms of the disease. However, applying the current standard criteria requires significant expertise and expensive equipment. Alternate screening methods for use in low-resource settings should be tested and considered for incorporation into public health programmes for the prevention and control of the disease.

There is clear evidence that the burden of RHD is high in developing countries and in indigenous and marginalised communities in some industrialised countries (Carapetis, 2007; Steer and Carapetis, 2009). Contemporary data from high-prevalence sentinel areas in diverse geographic locations are required to focus on baseline characteristics and gaps in the implementation of evidence-based intervention, as well as to quantify the morbidity and mortality rates associated with the disease in the current era. Comprehensive, prospective cohort studies of long-term outcomes are needed, from progression of the disease to the distal sequelae of RHD, such as stroke, AF and IE. This is of particular importance in low- and middle-income countries, where robust disease estimates, in the midst of the continuous burden of disease, will play a significant role in political and medical advocacy. This thesis addresses these needs and attempts to fill the gap in the current literature regarding contemporary outcomes of asymptomatic and symptomatic rheumatic heart disease, by utilising a new population-based model for RHD.

## 1.8 A new model of rheumatic heart disease: The RHD pyramid

The use of echocardiography as a screening tool has an important role to play in advocacy, education and awareness of RHD (Zühlke and Mayosi, 2013). However, using these prevalence estimates in computing overall disease figures carries the potential for an inaccurate description of the burden of disease. It is thus more accurate to review the classical pharyngitis-ARF-RHD paradigm and instead describe the disease burden with greater subtlety, taking into account the increasing understanding of the disease as well as public health implications. Such a revised model includes an assessment of RHD burden in two categories: 1) asymptomatic disease, or latent disease and 2) symptomatic disease, or active disease such as depicted in Figure 1.15 – a population model of assessing and reporting burden of rheumatic heart disease incorporating asymptomatic and symptomatic disease (Zühlke and Steer, 2013).

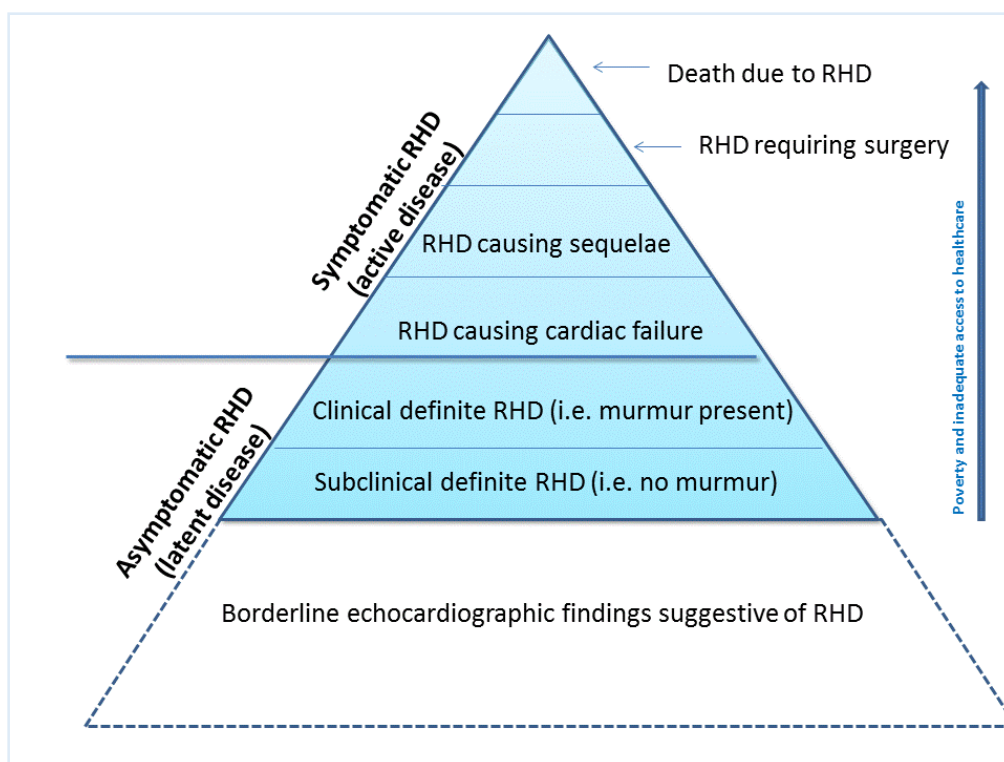


Figure 1.15. A population model for assessing and reporting burden of rheumatic heart disease incorporating asymptomatic and symptomatic disease (Zühlke and Steer, 2013)



This PhD thesis utilises this revised model to quantify the outcomes of symptomatic and asymptomatic RHD in Cape Town, South Africa, and in other developing and emerging economies. It focuses on the progression from one level of the pyramid to another and attempts to identify key characteristics, gaps in evidence-based interventions, and prognostic indicators that facilitate this progression.

## **1.9 Specific aims of the thesis**

The aims of this thesis are to:

1. Conduct a systematic review of the incidence, prevalence and outcomes of RHD in South Africa over the past two decades.
2. Document the long-term outcomes of subclinical carditis detected through a screening programme.
3. Validate computer-assisted auscultation and hand-held echocardiography for conducting screening in low-resource settings.
4. Present contemporary estimates of disease, detailing the baseline characteristics, prevalent sequelae and gaps in evidence-based implementation in a cohort of 3,343 children and adults from 12 African countries, India and Yemen.
5. Determine the incidence and prevalence of sequelae in 531 children and adults from Cape Town, South Africa, and explore independent predictors for mortality and morbidity.

## 2 Methods

In this section, I will be describing the methods used in the five inter-linked studies contained within this thesis. Firstly, I will provide a short introduction to the programme in which this thesis is embedded, followed by the detailed approaches used in each study.

### 2.1 Pan-african strategies to eliminate rheumatic heart disease in the 21<sup>st</sup> century-

The foci of traditional public health principles include infectious diseases, maternal and child health, and occupational and environmental exposures. Acute rheumatic fever (ARF)/rheumatic heart disease (RHD) fits very well into this model, as it is an infectious disease, is communicated in close environments and poses a particular risk to children and young adults. It is often referred to as a barometer of access to health care, and is indicative of social injustice and poverty (Brown et al., 2007). Yet, RHD also falls within the scope of non-communicable diseases. Beyond its prevention in terms of social development and improving access to basic health services, lie the primary prevention of streptococcal sore throat, the use of secondary prophylaxis as delivered within a registry-based programme, and tertiary cardiac services with surgery and interventions (Karthikeyan and Mayosi, 2009; McDonald et al., 2005). All of these fall within the realm of ‘traditional’ public health strategies.

However, ‘new’ public health principles, with an increasing emphasis on the complexity of health-related issues and the focus on interdisciplinary approaches, may well be the answer to controlling this disease and planning cost-effective and community-appropriate interventions to stem it in the countries that most need such a consolidated approach (Zühlke, 2011). The Awareness, Surveillance, Advocacy and Prevention (ASAP) programme is one such initiative, drawing on different disciplines to plan a multipronged approach to attacking this disease on all fronts, incorporating public health principles to target health promotion and prevent disease, while advocating appropriate interventions – backed by robust data (Engel et al., 2009b; Mayosi et al., 2006). The ASAP programme followed a call to action from key players in Africa’s healthcare and political realms, who have agreed to a pledge of action to reduce it, in response to the persistent health burden attributable to ARF/RHD (Mayosi, 2009). The efforts are targeted at raising awareness, establishing surveillance systems, advocating increased resources for treatment, and

promoting prevention strategies, using a community-based, bottom-up approach that rests on those four pillars. The ASAP programme has been an example of programmes initiated from, run by and organised by countries most affected by the disease (Colquhoun et al., 2009; Steer et al., 2009a).

The primary objective of this programme remains the creation of a simple, modular but comprehensive model for ARF/RHD control in Africa, building on the best evidence-based interventions; it will hopefully be adopted by national departments of health, as well as countries and organisations with a combined commitment to reducing the burden of disease attributable to ARF/RHD in Africa. Focusing on the four pillars of action in the fight against ARF/RHD will provide a framework for communities, politicians and physicians to work together to control this preventable disease from continuing to wreak havoc among the poor in the world. This doctoral dissertation is thus nested within major studies that are spearheaded by the ASAP programme in Cape Town.

## **2.2 Study 1: Systematic review of incidence, prevalence and outcomes of rheumatic heart disease**

Since 1994, there have been significant advances within the health care sector, with various new primary health care initiatives and a renewed focus on improved health care delivery. It is of interest to ascertain, using a predefined systematic review, whether these efforts have translated into a decreased RHD burden in the country. We thus propose to appraise the contemporary estimates of burden of RHD between 1994 and 2014, and to report on the fatal and non-fatal outcomes of RHD.

We chose a systematic review as the best format for this appraisal. A systematic review focuses on a particular research question (or questions), in order to identify, appraise, select and synthesise all the high-quality research evidence relevant to that question (or those questions). Although traditionally utilised for randomised control trials, observational studies provide important data and may well be the only design choice for certain exposures, and thus, a systematic review design can be utilised to best control for the confounding selection and publication biases (Sargeant et al., 2014). The findings are reported using the meta-analysis of observational studies in epidemiology (MOOSE) guidelines (Stroup et al., 2000).

Our primary objective is to review the current best estimates of the incidence of newly diagnosed cases, and the prevalence of existing RHD, using observational studies published within the past two decades. We also characterise the fatal and non-fatal outcomes of RHD, using case-fatality rates and cause-specific mortality rates, and we identify trends in the RHD burden over the past twenty years.

### **2.2.1 Methods**

This review protocol has been registered with the PROSPERO International Prospective Register of systematic reviews (<http://www.crd.york.ac.uk/PROSPERO>), under the registration number CRD42014007072.

### **2.2.2 Inclusion and exclusion criteria**

Any study reporting on the incidence or prevalence of RHD, that had been conducted in South Africa and published in English or Afrikaans between 27 April 1994 and 26 April 2014 was considered for inclusion. Upon further review, only studies where most of the patient population was recruited in the period April 1994-April 2014 were included.

There were no age restrictions used during the article retrieval process. We included any study that estimated one or more of the following epidemiological measures of RHD burden: incidence, prevalence, remission rate, relative risk of mortality (i.e., excess mortality), or cause-specific mortality. In addition, we considered any study of cardiovascular morbidity that quantified the attributable proportion of RHD cases. These, however, were limited to disaggregated data pertaining to RHD. The prevalence of RHD has in the recent past been defined by screening programmes of subclinical disease in asymptomatic populations (Saxena et al., 2013; Zühlke and Mayosi, 2013; Zühlke et al., 2013). Hospital-based studies, however, focus on clinical disease in symptomatic populations. As far as possible, we thus elucidated the diagnostic methods in both echocardiography screening studies and hospital-based studies. In the context of RHD, ‘remission’ is due exclusively to surgical intervention; thus, we explored the surgical literature for rates of disease regression versus long-term progression (i.e., leading to mortality). In our clinical experience, the following morbid outcomes are considered the most significant, and we thus include heart failure, ischaemic/thromboembolic or haemorrhagic stroke, atrial fibrillation (AF),

infective endocarditis (IE), and valve repair or replacement. In addition, we considered any study of cardiovascular morbidity that quantified the attributable proportion of RHD cases.

The burden of structural heart disease (including RHD) among South Africans seeking antenatal care was recently reviewed (Watkins et al., 2012) so, for the purpose of this review, we excluded studies of RHD in pregnancy. Studies were also excluded, if they focused on degenerative heart valve disease, rheumatological conditions other than RHD, or solely on ARF. As a rule, we also omitted autopsy and necropsy studies, because consent rates for these procedures in South Africa are low, and their conclusions about mortality patterns are highly likely to be biased. We immediately excluded editorials, commentaries, and case reports, except to hand-search their reference lists. While the World Health Organisation (WHO) recommends considering the inclusion of disease register data in burden-of-disease studies, rheumatic fever registers tend to exclude information regarding RHD – one of our outcomes – during the period of interest. They are thus excluded from our analysis. Similarly, the latest South Africa Demographic and Health Surveys (2003) do not contain primary data on RHD, and thus could not be reviewed (Department of Health- Director General of Health, 2003).

### **2.2.3 Search strategy**

Two clinician-researchers (LJZ, paediatric cardiology; DAW, internal medicine) compiled lists of articles obtained from three large databases relevant to the South African population: PubMed, ISI Web of Science, and EMBASE. Additionally, to identify South African conference proceedings, theses, and abstracts, we hand-searched the following archives at the University of Cape Town's Health Sciences Library: current and completed research (South Africa), SA Heart, and finally the database SAePub, which covers all South African publications, including those not currently indexed. The process was managed using EndNote X7® software. We also collected vital registration data from Statistics South Africa. Although the flaws in vital statistics are well-known, the Global Burden of Disease Study considers them an important source of mortality data, and incorporates specific methods for handling misclassifications and inconsistencies (Murray et al., 2012a). Finally, we hand-searched the reference lists of all studies included in the final review. Prior consultation with other RHD experts had led us to suspect a substantial amount of 'grey' literature on RHD. Thus, we intentionally kept the database search strategy broad and redundant. We communicated with other South African cardiovascular disease researchers and practitioners, as well as with international experts on RHD, when possible, to identify unpublished works or to

obtain additional information. Both published and unpublished data were subject to the same quality assessment. The pre-specified search strategy for each database was mentioned previously (see Tables 2.1 and 2.2).

The two researchers (LJZ and DAW independently) in the first instance, selected articles with relevant titles and abstracts, after which full-text manuscripts were obtained from potentially eligible reports. When discrepancies arose over the inclusion of titles/abstracts or full-text articles, we resolved them by consensus discussion between the two primary reviewers (LJZ and DAW), with arbitration by a third reviewer (MEE), where this was necessary

#### **2.2.4 Data extraction**

The primary reviewers used a standardised data extraction form to extract information from included articles that had been independently duplicated (i.e., not split between the two authors) in order to improve reliability. The data extraction form captured basic study characteristics, including objectives, study population, sample size, years and location of study, as well as study design. Disease-related parameters, including hospitalisation, secondary events, surgical interventions and mortality were recorded too. Where study data were unclear, the original author of the manuscript was contacted to clarify his or her findings. Where not provided, confidence intervals were incorporated into the formula,  $SE = (\text{upper limit} - \text{lower limit}) / 3.92$  or calculated using the `cii` command in STATA® 11.2. Where not stated, RHD mortality per 100,000 was calculated as follows:  $\text{RHD deaths} / \text{mid-year population}$ . Where population number was not stated, this was calculated by using age-specific incidence rates and cases stated in the original paper as follows:  $100,000 \times (\text{number of cases} / \text{incidence per } 10^5)$ .

Table 2.1. Search strategy

Database	Search terms	Limits
<b>PubMed</b>	(Search ((RHD [MeSH Major Topic]) OR RHD [Title/Abstract]) OR "rheumatic heart")) AND (((south african [MeSH Major Topic]) OR south africa [MeSH Major Topic]) OR south africa [Title/Abstract]))	Limited to English/Humans 1994-2014
<b>ISI Web of Science</b>	TS=RHD AND CU=SOUTH AFRICA	Limited to English/Humans 1994-2014
<b>EMBASE</b>	"Rheumatic heart" AND ("South Africa" OR "South African" OR "South Africans") Advanced: checked options for free-text search and explosion of terms	Limited to English/Humans 1994-2014
<b>Current and Completed Research</b>	TS: "RHD"	Limited to English/Humans 1994-2014
<b>SA theses (including Navtech and UCTD)</b>	TS: "RHD"	
<b>SA ePub</b>	"RHD"	
<b>SA Heart</b>	Hand-searched titles over 1994-2014	
<b>Statistics South Africa</b>	Searched all reports on causes of death in South Africa that were published in 1994-2014	

### 2.2.5 Quality assessment

For all studies that were deemed eligible for inclusion, we assessed the overall quality of the study according to four basic criteria: (1) representativeness of cases to the general population with RHD, (2) completeness of dataset (including follow-up), (3) validity of case definitions and methods of ascertainment, and (4) appropriateness of the study design to the research question. These criteria were adapted from the general criteria used in the Global Burden of Disease Study (Lim et al., 2012) and assigned one point on a four-point scale. For specific estimates reported in a study, we assigned each estimate a grade A, B, or C, based on the quality of the data and study methods. For instance, a population-based study of incidence would receive an “A”, a hospital-based study of incidence accounting for a catchment area would receive a “B”, and a study reporting rates of hospitalisation as incidence would receive a “C”. Again, we resolved discrepancies in data extraction or assessed the quality of study quality by consensus discussion between the two primary reviewers (LJZ and DAW), with arbitration by a third reviewer (MEE), where this was necessary.

### 2.2.6 Risk of bias assessment

We also included an assessment of risk of bias. The Cochrane collaboration suggests that the phrase “risk of bias” is the preferred terminology in reflecting the risk of underlying bias in study design or execution, in addition to the effect of exposure to intervention, while the study was in progress. The risk of bias was assessed using the design-specific criteria outlined in the publication by the Agency of Health-related Research and Quality, listed in Table 2.2. These permit the assessment of selection, performance, attrition, detection and reporting biases (Viswanathan et al., 2011).



Table 2.2. Design-specific criteria for risk of bias assessment

Risk of bias	Criterion	Cohort	Case-control	Case series	Cross -sectional
<b>Selection bias</b>	Were participants analysed within the groups to which they were originally assigned?	x			
	Did the study apply inclusion/exclusion criteria uniformly to all comparison groups?	x			x
	Were cases and controls selected appropriately (e.g., appropriate diagnostic criteria or definitions, equal application of exclusion criteria to case and controls, sampling not influenced by exposure status)?		x		
	Did the strategy for recruiting participants into the study differ across study groups?	x			
	Do the design and analysis controls account for important confounding and modifying variables through matching, stratification, multivariable analysis, or other approaches?	x	x	x	x
<b>Performance bias</b>	Did researchers rule out any impact from a concurrent intervention or an unintended exposure that might bias results?	x	x	x	x
	Did the study maintain fidelity to the intervention protocol?	x	x	x	
<b>Attrition bias</b>	If attrition (overall or differential nonresponse, dropout, loss to follow-up, or exclusion of participants) was a concern, were missing data handled appropriately (e.g., intention-to-treat analysis and imputation)?	x	x	x	x
<b>Detection bias</b>	In prospective studies, was the length of follow-up different between the groups, or in case-control studies, was the time period between the intervention/exposure and outcome the same for cases and controls?	x	x		
	Were the outcome assessors blinded to the intervention or exposure status of participants?	x	x	x	x
	Were interventions/exposures assessed/defined using valid and reliable measures, implemented consistently across all study participants?	x	x	x	x
	Were outcomes assessed/defined using valid and reliable measures, implemented consistently across all study participants?	x	x	x	x
	Were confounding variables assessed using valid and reliable measures, implemented consistently across all study participants?	x	x	x	x
<b>Reporting bias</b>	Were the potential outcomes pre-specified by the researchers? Are all pre-specified outcomes reported?	x	x	x	x

### 2.2.7 Data synthesis

Prevalence data from individual studies were combined using random-effects meta-analysis according to the Mantel-Haenszel method. Heterogeneity was evaluated using the  $\chi^2$ -based Q statistic (significant for  $P < 0.1$ ) and the  $I^2$  statistic ( $> 50\%$  to be indicative of “notable” heterogeneity) (Higgins and Thompson, 2002). STATA software, version 11.2 (STATA Corporation, College Station, Texas), was used to perform calculations and the meta-analysis, and to produce the forest plots using the metan routine.

### 2.2.8 Presenting and reporting of results

We used flow diagrams to summarise the study selection process and to detail reasons for exclusion. This follows the PRISMA guidelines for reporting systematic reviews (Moher et al., 2009). We plan to publish our search strategy and quality-scoring tool as supplementary documents to a final publication, outside of this thesis. Our protocol has previously been published (Zühlke et al., 2014b).

### 2.2.9 Outcomes

**Incidence:** We tabulated crude age-specific incidence estimates per 100,000 persons per year in summary tables, along with their 95% confidence intervals (CI). To estimate pooled median incidence rates and assess for heterogeneity, we fitted random effects models to log-transformed observed incidence in STATA ver. 11.2 (STATA Corp., TX). We obtained estimates of the median incidence and 25th and 75th percentiles of the distribution of true incidence by back-transforming the log estimates to the original incidence scale.

**Prevalence:** The pooled overall age-specific prevalence of RHD per 1,000 persons was calculated and expressed with a 95% CI, when appropriate. It is well known that, in screening for and diagnosing RHD, auscultation has limited sensitivity compared with echocardiography, which is the current reference test (Saxena, 2013). Therefore, we report only echocardiographically detected screening data, utilising the WHF criteria.

We expressed data on both fatal and non-fatal outcomes in the pooled analysis. We tabulated estimates of crude age-specific mortality rates from RHD per 100,000 persons per year, along with their 95% CIs. Attributable proportions and the relative risks of fatal and non-fatal outcomes were calculated when data were available, and 95% CIs were generated using the ‘cii’ command in STATA®. A measure of the consistency of results is included and, in cases where data were not amenable to meta-analysis, we present a narrative summary. Any trends are reported upon, either using meta-analytic methods such as meta-regression, if possible, or a detailed qualitative assessment.

## **2.3 Study 2: The natural history of asymptomatic rheumatic heart disease detected by echocardiography in schoolchildren**

The first screening study using first-line portable echocardiography was performed in Africa in 1996 (Anabwani and Bonhoeffer, 1996). Since then, a myriad of studies have demonstrated the superior sensitivity of echocardiography compared to auscultation in confirming the subtle valve changes that are consistent with subclinical RHD (Zühlke et al., 2013). The vast majority of these children are asymptomatic, suggesting a pre-symptomatic phase during which penicillin prophylaxis may be used to prevent recurrent attacks of rheumatic fever and potentially ameliorate the development of chronic RHD. In order to advocate screening on a large scale, however, there needs to be clear evidence that identifying these cases will improve prognosis (Zühlke and Mayosi, 2013). Long-term follow-up studies may provide the data to answer questions regarding the value of screening, the natural history of screen-positive valve lesions and the role of secondary prophylaxis for definite and borderline RHD.

### **2.3.1 The ASAP Programme**

Following the publication of a landmark article confirming the superiority of portable echocardiography over auscultation (Marijon et al., 2007), a screening study was conducted in the Vanguard community. The findings of the echocardiographic screening study of RHD in schoolchildren in the Vanguard community have been reported in the PhD thesis of Dr Mark Engel (Engel, 2012). This study reports on the medium-term follow-up of schoolchildren who were determined to have borderline or definite disease when they were screened during the 2008-2012 period.

### 2.3.2 Setting

This report is based on a surveillance study of RHD that was conducted in the Vanguard communities (i.e., Bonteheuwel and Langa townships) of Cape Town in South Africa from January 2008 through March 2012 (the period of recruitment). The period of follow-up began in January 2008 with the enrolment of the first participant to September 2014 when the last participant was followed-up. The scoring of the enrolment and follow-up echocardiograms according to the WHF criteria occurred in August 2013 through September 2014 (Table 2.3).

The study was conducted in adjacent residential areas of Bonteheuwel and Langa with a total population of 55 707 and 49 667, respectively. The majority of the population of Bonteheuwel is of mixed ancestry, whereas the predominant population of Langa is black African. The population of Langa has noticeably poorer socioeconomic indicators compared with Bonteheuwel based on proportion of households with an income <US\$200 per month (71.5% vs 36.1%;  $p<0.05$ ), households with piped water inside the dwelling (35.4% vs 84.1%;  $p<0.05$ ) and number of non-brick dwellings (49.7% vs 11.5%;  $p<0.05$ ).

Table 2.3. Reclassification of all definite and probable disease.

	Original Classification (adapted NIH criteria)			WHF Classification		
	Cases	prevalence[ 95% CI]		Cases	prevalence[ 95% CI]	
<b>Vanguard cohort total</b>						
Definite	16	5.9	[3.3-9.5]	Definite	13	4.0 [2.0-7.2]
Probable	62	22.8	[17.5-29.1]	Borderline	42	15.4 [11.1-20.8]
Total RHD	78	28.7	[22.7-35.7]	Total RHD	55	19.5 [14.6-25.4]
<b>Langa</b>						
Definite	11	8.4	[4.2-15.1]	Definite	10	6.2 [2.9-11.8]
Probable	39	29.9	[21.4-40.7]	Borderline	29	20.1 [13.5-28.8]
Total RHD	50	38.4	[28.6-50.2]	Total RHD	38	26.4 [18.7-36.0]
<b>Bonteheuwel</b>						
Definite	5	3.5	[1.1-8.2]	Definite	3	1.6 [0.2-2.0]
Probable	23	16.2	[10.3-24.3]	Borderline	13	10.2 [5.4-17.3]
Total RHD	28	19.8	[13.2-28.4]	Total RHD	15	11.7 [6.6-19.3]

Prevalence expressed per 1,000 population. Acronyms: NIH – National institutes of Health; RHD – Rheumatic Heart Disease; WHF – World Heart Federation.

### 2.3.3 Participants

The schoolchildren were entered into the echocardiographic surveillance study by use of random sampling methods by class and school in each Vanguard community. Briefly, the sampling process was conducted in three stages: stratification by residential area (i.e., Bonteheuwel and Langa), then by school grade, and then simple random selection of classrooms. All schoolchildren in a selected classroom were invited to participate, and the parents/guardians were asked to sign a consent form and provide information pertaining to past medical history. Echocardiographic scanning at enrolment was conducted by a trained echocardiographer using a portable echocardiography machine in a mobile clinic. Images were stored for review as indicated above.

The participants with abnormal echocardiograms based on the modified NIH criteria were entered into this study. These participants were contacted for a follow-up echocardiogram, and a comprehensive clinical examination was performed by a paediatric cardiologist (LJZ). Learners with definite RHD on echocardiogram or a clinical murmur were referred to a local clinic for secondary antibiotic prophylaxis. At each visit, learners were advised to bring long a signed prophylaxis sheet to verify adherence to prophylaxis.

An intensive effort was made between August 2013 and September 2014 to arrange a follow-up echocardiographic examination for schoolchildren with abnormal echocardiograms according to the WHF criteria, whether they had attended their follow-up clinic or not. The participants were classified into the following diagnostic categories based on the review of the enrolment and follow-up echocardiograms: persistors (i.e., diagnostic category unchanged), progressors (i.e., worsened, e.g., from borderline to definite) or regressors (i.e., improved, e.g., definite to borderline or borderline/definite to normal).

### 2.3.4 Variables and measurement

The echocardiographic variables of interest in this study were the presence of pathological mitral regurgitation (MR) and aortic regurgitation (AR), mitral stenosis (MS), and morphological features of RHD on the mitral and aortic valves. These variables were initially used to classify participants at enrolment into definite RHD, probable RHD, possible RHD or no RHD (normal) as defined by the modified NIH criteria (Zühlke and Mayosi, 2009). When the WHF criteria became available

towards the end of the study, the baseline and follow-up echocardiograms were reclassified accordingly (Remenyi et al., 2012a).

### **2.3.5 Bias**

Several measures were taken to minimise bias in this study. Firstly, the random ascertainment of the participants in the surveillance sought to ensure the generalizability of finding to schoolchildren in the Vanguard communities. Secondly, all available participants with abnormal enrolment echocardiograms were invited to participate in the follow-up study. The study size was therefore based on the number of participants with abnormal echocardiograms who were identified at the time of original ascertainment. Finally, one observer applied the WHF criteria to the baseline and follow-up echocardiograms, with verification of findings by a second observer.

### **2.3.6 Study design**

This is a prospective study of the natural history of latent RHD that was diagnosed by echocardiography during the course of a surveillance of study in schoolchildren. The study was approved by the Departments of Health and Education of the Western Cape Government, and Human Research Ethics Committee of the Faculty of Health Sciences of the University of Cape Town. All participants gave written parental consent and individual assent prior to the enrolment echocardiogram.

The modified National Institutes of Health (NIH) criteria that were used at enrolment allocated the participants into four categories: definite RHD, probable RHD, possible RHD or normal study (Zühlke, 2009). The enrolment echocardiograms were acquired by two echocardiographers who scored them at time of acquisition (CEL and MvdW) and confirmed by a cardiologist (LJZ). Pairwise kappa test showed fair agreement between the echocardiographic technician and the cardiologist (agreement, 93.11%;  $\kappa = 0.3$ ; SE = 0.0329).

The abnormal enrolment echocardiograms were re-classified when the WHF criteria became available in 2012 (Remenyi et al., 2012a). All schoolchildren with latent RHD according to the WHF criteria were invited for a follow-up echocardiogram which was acquired by one examiner (LJZ) and scored according to the WHF criteria. The WHF criteria were also applied to the

enrolment and follow-up echocardiograms by a second reader (AM, CEL, MB, or MvdW) before final classification into definite RHD, borderline RHD or normal study. The overall agreement for definite disease (the primary endpoint) was fair (kappa 0.69 (95% CI 0.65 to 0.73). All readers were trained in the application of the WHF criteria using a training set of echocardiograms.

### **2.3.7 Statistical methods**

Variables were described by use of the mean, median, standard deviation and interquartile range, where appropriate. Univariable relationships were explored using cross-tabulations and frequencies were calculated. Linear and multivariable regression was used to identify independent predictors of diagnostic category at follow-up. All data were managed in the Department of Medicine at the University of Cape Town using Epi-Info software, and Stata Version 11.2 (Cary, NC, USA) was used for the analysis.

### **2.3.8 Aims**

This follow-up study aimed to assess the natural history of asymptomatic RHD after 3-5 years of follow-up, utilising the WHF criteria for echocardiographic diagnosis of RHD.

## **2.4 Study 3: Alternative modalities of screening for asymptomatic rheumatic heart disease**

Recent studies from Africa, Asia, Australasia and Oceania have highlighted the high prevalence of asymptomatic RHD in schoolchildren using echocardiography (Anabwani and Bonhoeffer, 1996; Ba-Saddik et al., 2011; Beaton et al., 2012; Bhaya et al., 2010; Carapetis et al., 2008; Marijon et al., 2006; Marijon et al., 2007; Paar et al., 2010; Saxena et al., 2011). However, it is still uncertain which is the most feasible and appropriate echocardiographic protocol for undertaking RHD screening in resource-poor settings (Carapetis and Zühlke, 2011). Given the high burden of disease (Zühlke et al., 2013), however, it is clear that those living in low-income countries require simple, affordable and reliable approaches to large-scale RHD screening.

Over the past decades, the demise of clinical auscultation as a screening and diagnostic tool in medicine has been noted with dismay (Dolara, 2008). The qualitative nature of this practice, combined with inadequate training and of late, inadequate skills, may limit the ability of clinicians to detect and diagnose abnormalities using this method alone. Reports have recently confirmed



the poor sensitivity and low positive predictive value of auscultation used in screening for RHD (Cramp et al., 2012; Roberts et al., 2013c; Webb et al., 2011) and as such, there are recommendations that the stethoscope be abandoned as the primary screening modality (Grimaldi et al., 2012; Marijon et al., 2008). Yet, previous auscultation-based screening studies (McLaren et al., 1975) and recent studies based on the more stringent WHF criteria (Colquhoun et al., 2014; Roberts et al., 2013c) show similar prevalence rates, suggesting that the latter studies (and by inference the former) may reflect true disease.

Computer-assisted auscultation (CAA) utilises a digital stethoscope together with an objective computer-algorithm to identify pathological murmurs; this could potentially improve the sensitivity and positive predictive value of standard auscultation. In addition, CAA is cheap, easily accessible and can be taught to all health practitioners for use in remote and poorly resourced conditions. We hypothesise therefore that CAA may be sufficiently sensitive and specific for detecting definite RHD.

Table 2.4. Alternate methods of screening for rheumatic heart disease

Screening method	Reference	Sample Size	Time taken to complete echo	Reviewer */operator#	Criteria	Sensitivity and/or specificity
Screening using abbreviated echocardiography protocols	Marijon et al.	3,677	NS	paediatric cardiologist*#	Abbreviated protocol§	
	Reeves et al.	362	5 minutes	paediatrician*/registrar#	WHO/NIH 2005	
	Beaton et al.	4,869	2 minutes	paediatric cardiologist*#	WHO/NIH 2005	
Screening using non-cardiologist reviewers	Reeves et al.	362	as above	paediatrician*/registrar#	WHO/NIH 2005	
Nursing reviewers	Colquhoun et al.	50	NS	nurse*#	mitral regurgitant jet>1.5cm§	Sensitivity: 100%, 83% Specificity: 67.4%, 79%
Hand-held echocardiography	Beaton et al.	125	NS	paediatric cardiologist*#	modified WHF criteria§	Sensitivity: 90.2% Specificity: 92.9%

Acronyms: NIH – National Institutes of Health; WHF – World Heart Federation; WHO – World Health Organisation; NS– not stated

The method used for detecting RHD in screening studies of asymptomatic children has changed progressively over the past two decades, from auscultation to different portable echocardiography protocols. These have included abbreviated protocols with standard portable machines, nurse-led screening and ultra-portable echocardiography with modified WHF criteria (Beaton et al., 2014a; Colquhoun et al., 2013; Reeves et al., 2011). Our method aims to extend the use of shortened echocardiography protocols, rapid screening times and non-cardiologist-led screening programmes (Table 2.4). FOCUS (A **FOCUS**ed method **U**tilising hand-held echocardiography in **S**creening for Rheumatic Heart Disease) is a method, which utilises one view (parasternal long-axis) and one measurement (measurement of mitral regurgitant jet), involving less than one minute of screening time. We hypothesise that this even simpler protocol using the single mitral regurgitation jet-length criterion of Mirabel et al. (Mirabel et al., 2012b) with a hand-held ultra-portable echocardiogram will have sufficient sensitivity and specificity in detecting definite and borderline RHD.

#### **2.4.1 Study population**

The original echocardiographic screening study of latent rheumatic heart disease was conducted on a random sample of 2,720 schoolchildren from the Vanguard communities of Cape Town, which are made up of the two suburbs of Bonteheuwel (n 1,303) and Langa (n 1,417). Following the previous rheumatic heart disease screening at this site, a nested case-control study commenced in August 2013 and continued until September 2014. Cases were schoolchildren previously diagnosed as having asymptomatic rheumatic heart disease using screening echocardiography. These were either definite or borderline cases of rheumatic heart disease according to the World Heart Federation criteria (Table 2.5). The controls were normal healthy schoolchildren previously enrolled in the screening study – thus matching for age, school grade and suburb. Cases and the controls involved in this study were contacted and invited to a research clinic at Groote Schuur Hospital. The single reviewing physician (LJZ) was blinded to their echocardiographic status. This study was approved by the Human Research Ethics Committee of the University of Cape Town, and the Departments of Health and Education of the Western Cape Government (Engel et al., 2009a).

Table 2.5. World Heart Federation Guidelines  
(Remenyi et al., 2012a)

Echocardiographic Criteria for Individuals Aged $\leq 20$ Years	
Definite RHD (A, B, C, or D)	
A. Pathological MR and at least 2 morphological features of RHD of the MV	
B. MS mean gradient $\geq 4$ mm Hg	
C. Pathological AR and at least 2 morphological features of RHD of the AV	
D. Borderline disease of both the AV and the MV	
Borderline RHD (A, B, or C)	
A. At least 2 morphological features of RHD of the MV without pathological MR or MS	
B. Pathological MR	
C. Pathological AR	
Criteria for Pathological Regurgitation	
Pathological mitral regurgitation	Pathological aortic regurgitation
(All 4 Doppler echocardiographic criteria must be met)	
Seen in 2 views	Seen in 2 views
In at least 1 view, jet length $\geq 2$ cm	In at least 1 view, jet length $\geq 1$ cm
Velocity $\geq 3$ m/s for 1 complete envelope	Velocity $\geq 3$ m/s in early diastole
Pan-systolic jet in at least 1 envelope	Pan-diastolic jet in at least 1 envelope
Morphological Features of RHD	
Features in MV	Features in AV
AMVL thickening $\geq 3$ mm (age-specific)	Irregular or focal thickening
Chordal thickening	Coaptation defect
Restricted leaflet motion	Restricted leaflet motion
Excessive leaflet tip motion during systole	Prolapse
These have been summarized for the purposes of this review. Please see the full referenced article for important explanatory notes and caveats. AMVL, anterior mitral valve leaflet; AR, aortic regurgitation; AV, aortic valve; MR, mitral regurgitation; MS, mitral stenosis; MV, mitral valve; RHD, rheumatic heart disease. Adapted, with permission, from Remenyi et al. [27].	

## 2.4.2 Methods

### *Recording heart sounds using computer-assisted auscultation and the Zargis cardioscan system*

Participants were examined in a quiet room. They were first examined for the presence of pathological murmur using a standard stethoscope, and then subjected to computer-assisted auscultation. When using the Zargis® system, auscultation was performed using a Bluetooth Littman® electronic stethoscope. The heart sounds and, if present, murmurs were transmitted to a receiving computer loaded with the Cardioscan® software. The heart sounds were recorded at four positions for 20 seconds at each site (i.e., mitral, tricuspid, pulmonary and aortic areas). The software analysed the recordings for up to one minute and then displayed findings as abnormal or normal as shown in Figure 2.1. Computer-assisted auscultation findings were stored on a password-controlled netbook in .zac files for the Zargis® system. These files were downloaded to a portable hard-drive for storage and analysis.

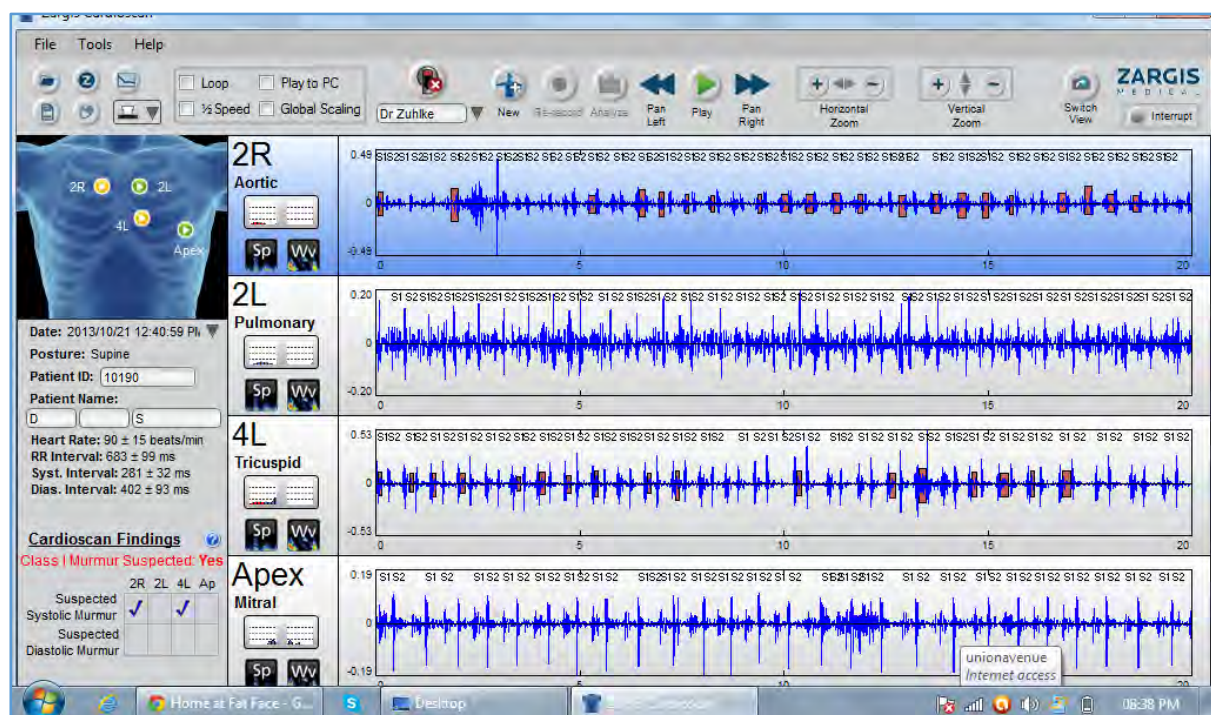


Figure 2.1. Zargis user interface in the case of an abnormal murmur being detected

### *Abbreviated echocardiography protocol utilising hand-held echocardiography*

The cases and healthy controls underwent the focused echocardiography protocol on the ultra-portable hand-held machine, followed by a full echocardiogram using a standard portable machine (Philips CX 50). A single operator (LJZ) performed all echocardiograms. The focused echocardiography protocol measured a single mitral regurgitation jet length of  $\geq 2$  cm seen in the long-axis parasternal view. This was noted independently of its velocity or duration during the heart cycle, and regardless of any morphological valve changes. The mitral regurgitation jet-length was measured from the vena contracta to the last pixel of the regurgitant colour Doppler map using the V-Scan radius measuring tool. A measurement where the mitral regurgitation jet-length was  $\geq 2$  cm constituted a positive result as demonstrated in Figure 2.2. The echocardiograms were scored according to the focused protocol as rheumatic heart disease screen positive or negative. All participants also underwent a comprehensive echocardiogram on a portable echocardiography machine and were categorised using the World Heart Federation criteria to confirm definite or borderline rheumatic heart disease or a normal finding (Remenyi et al., 2012a).

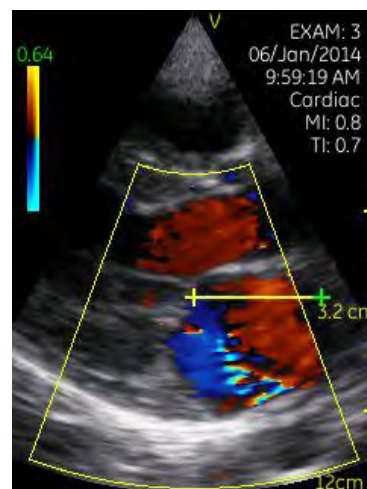


Figure 2.2. Screen positive mitral regurgitation jet

### **2.4.3 Statistical methods**

The clinical characteristics of the participants were described as mean and standard deviations (SD) for normally distributed data, and as medians and interquartile ranges (IQR) for skewed data. A sample size of 75 participants would determine the proportion of patients, with 95% confidence and a precision of greater than 1%. A sensitivity of greater than 90% is acceptable for a screening test (Akobeng, 2007; Glas et al., 2003; Zhou. et al., 2011). We also computed the diagnostic odds ratio, as it is a single measure of effectiveness of a diagnostic test independent of prevalence (Glas

et al., 2003). A diagnostic odds ratio of greater than one is indicative of a discriminatory test, while a diagnostic odds ratio that is greater than 400 indicates an acceptable effect size.

The focused protocol recorded findings as normal or rheumatic heart disease screen positive, while the computer-assisted auscultation results were scored as either normal or abnormal. The sensitivity and specificity of both tests to detect participants with definite and borderline rheumatic heart disease (together and separately) are reported with the echocardiographic diagnosis of rheumatic heart disease as the standard reference, utilizing the full World Heart Federation criteria on images acquired by means of a standard portable echocardiography machine. Sensitivity and specificity analyses were calculated using contingency tables. 95% confidence intervals were calculated using the “cii” command in STATA, and positive and negative predictive values for the alternative screening modalities were determined, along with the reliability (or percentage correct) of the test. In the cases where the sensitivity or the specificity equalled zero, the contingency tables were all adjusted by adding 0.5, according to the method described by Glas et al. (Glas et al., 2003) to report the diagnostic odds ratio.

All statistical tests were two sided at  $P = 0.05$ . Data were captured into an Epi Info® database (CDC, Atlanta, Georgia, USA) and analysed using STATA® version 12 (StataCorp LP, Station Road, Texas, USA). The standards for reporting of diagnostic accuracy studies (STARD) and strengthening the reporting of observational studies in epidemiology (STROBE) criteria were used for analysis and reporting of this study (Bossuyt et al., 2003; Vandembroucke et al., 2014).

#### **2.4.4 Aims**

The aims of this study are:

- To determine the sensitivity and specificity together with the likelihood ratios and predictive values for CAA in determining subclinical RHD, when compared with portable echocardiography and the full WHF criteria.
- To determine the sensitivity and specificity together with likelihood ratios and predictive values for a focused short protocol and hand-held echocardiography in determining subclinical RHD, when compared with portable echocardiography and the full WHF criteria.



## 2.5 Studies 4 and 5: The clinical characteristics, treatment and outcome of symptomatic rheumatic heart disease – The Global Rhematic Heart Disease Registry (The REMEDY Study)

The Global Rhematic Heart Disease registry (The REMEDY Study) was designed to assemble a contemporary prospective cohort of RHD patients to evaluate disease and treatment patterns, with particular emphasis on valvular involvement, the prevalence of adverse cardiac events and pharmacological treatments used particularly secondary antibiotic prophylaxis and oral anticoagulation therapy. The pilot phase of this registry involves cardiology sites from Africa, Yemen and India.

### 2.5.1 Study design and participants

The rationale and design of REMEDY have previously been published in full (Karthikeyan et al., 2012a). REMEDY enrolled 3,343 hospital-based patients from 26 different sites in Africa (24) Yemen (1) and India (1), representing 14 different countries where RHD is endemic. The sites fell into three World Bank income categories: low-income (Ethiopia, Malawi, Mozambique, Rwanda, Kenya and Uganda), lower-middle income (Egypt, India, Nigeria, Zambia, Sudan and Yemen) and upper-middle income (Namibia and South Africa). In addition, five of our sites were in heavily indebted, poor countries (Ethiopia, Mozambique, Rwanda, Uganda and Zambia). See Appendix 10.8. Sites were chosen based on previous collaborations and commitment to the project.

### 2.5.2 Study organisation and data collection

Patients were enrolled using designated case record forms (CRF) as listed in Appendices 10.6 and 10.7. Data were captured regarding diagnosis, and baseline clinical and echocardiography findings. These were relayed using the Datafax system to the Population Health Research Institute at McMaster University, Canada, which is the global collaborating centre on REMEDY. The principal co-ordinating office was based in the Department of Medicine at the University of Cape Town, in South Africa. Information was obtained through patient interviews and verified by chart review when possible. A detailed echocardiographic assessment was performed to characterise and quantify the severity of valvular involvement. The American Heart Association (AHA)/American College of Cardiology (ACC) guidelines for the assessment of the severity of valve lesions were used as a guide (Bonow et al., 2008; Nishimura et al., 2008; Nishimura et al., 2014). The REMEDY



database contained prospectively collected data on clinical and demographic diagnoses, comprehensive echocardiographic assessments and detailing of cardiovascular events. These were recorded at baseline and then at 12 months and 24 months. Data were reviewed for quality, and inconsistencies were resolved by referring to the source data at referring sites.

### 2.5.3 Statistical methods

#### *Sample size*

With a sample size of 3,000 patients, followed up for 2 years, the main study seeks to determine the rates of all outcomes individually with 95% confidence intervals and a precision greater than 1%. In this thesis, I will report outcomes for the two sites linked to the University of Cape Town which were the first to achieve a 100% 2-year follow-up rate in October 2014. The reported dataset for the follow-up component is the subset from two of the sites. The schedules of visits and the minimum recommended study procedures are shown in Table 2.6.

Table 2.6. Visit schedules and recommended study procedures

<b>Data collected</b>	<b>Visit 0</b>	<b>Visit 1 (12 months)</b>	<b>Visit 2 (24 months)</b>
<b>Informed consent</b>	X		
<b>Medical history and physical examination</b>	X	X	X
<b>ECG</b>	X*	X*	X*
<b>Echocardiography</b>	X	X	X
<b>Assessment for outcome event</b>		X	X
<b>Blood tests</b>	X**	X**	X**

\* Performance of ECGs at each follow-up visit is not mandated, but data will be collected if done as part of routine practice.

\*\* Including INR (international normalised ratio). Data will be collected if tests are done as part of routine practice.

### *Outcome measures for the follow-up component*

The outcomes of interest are death, congestive heart failure, stroke, transient ischaemic attack, non-central nervous system systemic embolism, major bleeding, new onset AF or atrial flutter, IE, pregnancy, valve surgery, percutaneous valvular interventions, and prosthetic valve thrombosis, as previously defined in Table 2.7 (Karthikeyan et al., 2012a).

Table 2.7. REMEDY event definitions

(Karthikeyan et al., 2012a)

Outcome	Definition
Death	Death due to any cause
Congestive heart failure	Any 2 of the 3 following criteria: (i) signs (rales, increased jugular venous pressure or ankle edema) or symptoms (dyspnea on exertion or at rest, orthopnea, nocturnal paroxysmal dyspnea, or ankle edema) of congestive heart failure, (ii) radiologic signs of pulmonary congestion, and (iii) treatment with diuretics
Stroke	Diagnosis of stroke by a physician based on sudden onset of neurologic deficit consistent with ischemia/infarction of a vascular territory, lasting $\geq 24$ h, with or without confirmation by neuroimaging
Transient ischemic attack	Deficits diagnosed by a physician lasting $< 24$ h
Non-CNS systemic embolism	Diagnosed clinically in patients with loss of arterial pulse and/or evidence of end-organ ischemia (eg, ischemic limb pain, gangrene, etc) with or without confirmation by Doppler studies or arteriography
Major bleeding	Bleeding that (i) is fatal, (ii) involves a critical site (intracranial, retroperitoneal, intraspinal, intra ocular, pericardial, or intra-articular), or (iii) leads to a reduction in hemoglobin level $\geq 2$ g/dL, or requires transfusion of $\geq 2$ units of whole blood or packed red cells
New-onset AF or flutter	Physician diagnosis with or without ECG evidence of AF or flutter
ARF	Diagnosed by the current WHO criteria <sup>25</sup>
Infective endocarditis	Diagnosed by the modified Duke criteria <sup>26</sup>
Valve surgery	Performance of any valve repair, or replacement of valve with a tissue, or mechanical prosthesis
Percutaneous valvular interventions	Percutaneous balloon dilatation of stenosed mitral, aortic tricuspid, or pulmonary valves
Prosthetic valve thrombosis	Recent onset ( $\leq 2$ wk) symptoms of valve dysfunction (dyspnea, angina, or congestive heart failure) accompanied by new onset of restricted valve leaflet motion on cinefluoroscopy with or without increased valve gradients on Doppler echocardiography <sup>27</sup>

CNS indicates Central nervous system; WHO, World Health Organization.

### *Role of co-ordinator*

The author was one of the co-authors of the rationale and design paper and contributed significantly to the final protocol. She co-ordinated and managed the entire study, performed all the data analysis after setting up the project. All training and co-ordination was done under her leadership and organisation.

### *Analysis*

Demographic characteristics were described using univariable summary statistics, such as means, proportions and standard deviations. These were stratified as appropriate by age, sex or site.

Continuous variables were expressed as means/medians, and standard deviations or interquartile ranges as appropriate. Categorical variables were expressed as frequencies and percentages. Associations between categorical variables were assessed for statistical significance using the Chi-squared test, and the unpaired t-test was used to determine group differences for continuous variables. For the baseline data, standard errors were adjusted using the survey command.

Outcome data were collected at the end of the 2-year follow-up period. All outcome events were summarised individually, as proportions and rates per 1,000-person years. Actuarial survival was calculated by means of the Kaplan-Meier method. Comparisons of baseline and outcome variables were performed using Students t tests or Chi tests as appropriate. The association of the baseline variables and adverse cardiovascular events were tested using a Cox proportional hazard regression analysis, following checking for colinearity prior to the univariate analysis. Univariable and multivariable models were fitted to identify risk factors associated with mortality, focusing on baseline variables, outcomes variables and combinations. Statistical significance was defined as a two-sided  $P < 0.05$ . Statistical analyses were performed using STATA 11®, STATA Corp, College Station Texas.

#### **2.5.4 Specific objectives of the REMEDY study: Baseline**

The baseline report of REMEDY addressed three objectives of the study:

1. The demographic characteristics of the affected patients and their presenting features, with particular reference to the pattern and severity of valvular involvement, the prevalence of AF, and other complications of RHD;
2. The pharmacological treatments used, particularly secondary antibiotic prophylaxis, oral anticoagulation therapy, and antiarrhythmic therapy for AF; and
3. A comparison of regional differences in the use of percutaneous and surgical interventional procedures.

### 2.5.5 Specific objectives of the REMEDY study: Follow-up

The follow-up report of the Cape Town REMEDY cohort addresses the following objectives:

1. The measurement of the prevalence and incidence of the sequelae of RHD over 2 years of follow-up in 531 Cape Town patients.
2. The determination of the annual mortality rate of patients with RHD in Cape Town.
3. The identification of independent predictors of mortality over a two-year follow-up period.
4. The description of the pharmacological treatments used, particularly secondary antibiotic prophylaxis and oral anticoagulation therapy and review patterns of adherence to secondary prophylaxis over the two-year period.

## 2.6 Summary

In these first two chapters, I have summarised the relevant literature relating to outcomes of symptomatic and asymptomatic rheumatic heart disease and detailed the methods involved in the five inter-connected studies conducted in this research. The subsequent chapters chronicle the specific studies and detail their findings.

In Chapter 3, I present the findings of a systematic review looking at the incidence, prevalence and outcomes of rheumatic heart disease over the past two decades. In Chapter 4, I report on the natural history of asymptomatic rheumatic heart disease as detected by screening echocardiography, and in Chapter 5, I report on alternate screening modalities. In Chapter 6, I describe the baseline findings of rheumatic heart disease in low- and middle-income countries and finally, in Chapter 7, I document the contemporary mortality and morbidity of 531 adults and children with RHD in Cape Town, South Africa. Lastly, I discuss the implications of this thesis for practice and research and outline the novel contributions of this work.

### **3 Study 1: Incidence, prevalence and outcomes of rheumatic heart disease in South Africa: A systematic review of contemporary studies**

#### **3.1 Abstract**

##### *Introduction*

Twenty years after its first democratic election, South Africa is experiencing a health transition. The impact of change on the incidence, prevalence and outcome of rheumatic heart disease (RHD) is unknown.

##### *Methods*

We conducted a systematic overview of the incidence, prevalence and outcomes of RHD in South Africa over the past two decades according to a published protocol.

##### *Results*

The overall crude incidence of symptomatic RHD was 24.7 per 100,000 (95% CI 22.1 to 27.4) population per annum amongst patients older than 13 years in Soweto, whilst the prevalence of asymptomatic echocardiographic RHD in schoolchildren was 20.2 cases per 1,000 children (95% CI 15.3 to 26.2) in Cape Town. The 60-day mortality after admission with acute heart failure due to RHD was 24.8% (95% CI 13.6% to 42.5%) and 180-day mortality was 35.4% (95% CI 21.6% to 54.4%). The combined effect size of 30-day mortality post-operatively was 2% (95% CI 0.0% to 4%; I<sup>2</sup>, 66.7%), (three studies, 1,089 participants). Single reports show post-surgical survival of over 75% at 5 years, and of over 70% at 10 years. Mortality rates per 100,000 population showed a decrease from 1.27 (95% CI 1.17 to 1.39) in 1997 to 0.7 (95% CI 0.63 to 0.78) in 2012.

##### *Conclusions*

The incidence of symptomatic RHD in adults and prevalence of asymptomatic RHD in schoolchildren are high in South Africa. Mortality was high in patients with RHD-related heart failure, although post-surgical morbidity and mortality were low. Mortality attributed to RHD may be falling at a population level.

## **3.2 Introduction**

Rheumatic heart disease (RHD) is responsible for a significant burden of cardiovascular morbidity and mortality, and remains the most common cause of acquired heart disease in children, adolescents and young adults in developing countries. RHD was long thought to have its hotspot in Africa South of the Sahara (Carapetis et al., 2005). Data from Johannesburg (1976) and Cape Town (1981) showed a prevalence of ~ seven per 1,000 in schoolchildren by cardiac auscultation (Bundred, 1986; McLaren et al., 1975). Surgical reports from the pre-1994 era reported significant morbidity and mortality of up to 8% per year, especially in the young (Antunes, 1992, 1997). The region Africa south of the Sahara has, however, seen significant change in the past decades, with the pace of per capita income growth in developing economies accelerating rapidly, substantially above that of advanced economies (Milanovic, 2012).

South Africa, a major economic force in this region, has undergone significant socio-political changes since the transition to democratic leadership and the first free elections in 1994. Since 1994, there have been substantial improvements in access to primary health care (Mayosi et al., 2012). Beyond the elimination of legislated racial policies, advances in South Africa during the past twenty years include substantial economic growth, the expansion of the black African middle class, and a greatly increased number of social grants to the very poorest and unemployed (Mayosi and Benatar, 2014). As RHD may be viewed as a barometer of access to primary health care and social justice (Brown et al., 2007), it is of interest to ascertain whether the social progress of the last twenty years has translated into a change in the burden of RHD in South Africa.

We conducted a systematic review of the literature of the incidence of newly diagnosed RHD, and the prevalence of RHD and summarised the data on fatal and non-fatal outcomes of RHD in South Africa since 1994.

## **3.3 Methods**

The protocol for this study has been published (Zühlke et al., 2014b) and is registered on PROSPERO (International Prospective Register of systematic reviews, registration number CRD42014007072, <http://www.crd.york.ac.uk/PROSPERO>). Section 2.2 in Chapter 2 describes the detailed methods.

### 3.4 Description of studies

#### *Results of the search*

Figure 3.1 shows the results of the search strategy. Of the 357 articles identified by the various search engines, following the removal of duplicates, 287 were excluded based on their titles, and 45 publications were excluded on examination of their abstracts. In addition, we included ten reports from Statistics South Africa (Statistics South Africa, 2005, 2006, 2007, 2008, 2009, 2010, 2011, 2012, 2013, 2014b), resulting in 35 articles needing full text evaluation. Table 3.1 shows studies that were excluded from the review.

#### *Characteristics of included studies*

Sixteen reports met the inclusion criteria, including 10 reports on mortality, four publications on morbidity, and one article each reporting on the incidence and prevalence of RHD (Figure 3.1; Table 3.2). The incidence and morbidity studies were conducted in tertiary hospital settings (Table 3.3). Engel et al. conducted a school-based prevalence study in a peri-urban setting from 2008 to 2012 (Engel, 2012). Revised data using the WHF criteria were provided by Dr Engel for this review (Engel et al., 2015). The Heart of Soweto study detailed new diagnoses of patients presenting to Chris Hani Baragwanath hospital from 2006 to 2008. The population of Soweto was estimated at 1.1 million. The Sub-Saharan Africa Survey of Heart Failure (THESUS-HF) study was a prospective, multicentre, international observational survey conducted in 12 cardiology centres from nine countries in the southern, eastern, central, and western regions of sub-Saharan Africa, for which the South African data were provided by the corresponding author (Damasceno et al., 2012). This study did not report on the details of the RHD diagnosis, such as length of diagnosis, valve involvement or surgical status.

Three reports detailed the long-term outcomes of surgical patients (Table 3.4). Barnard (Barnard et al., 2010) reported on the five-year follow-up of RHD patients undergoing isolated mitral valve replacement. Geldenhuys (Geldenhuys et al., 2012) and Ogunrombi (Ogunrombi, 2011) reviewed surgical outcomes in patients undergoing surgery. Only data on the RHD patients were included in this review. We found ten vital statistics reports, which detailed cause-specific mortality and death rates in South Africa from 1997 to 2012 (Statistics SA's Mortality and Causes of Death in South Africa Report for 2011, 2014; Statistics South Africa, 2005, 2006, 2007, 2008, 2009, 2010,

2011, 2012, 2013, 2014a) The total number of RHD deaths was reported utilising ICD 10 coding, where RHD was listed as a major cause of death or contributor to death.

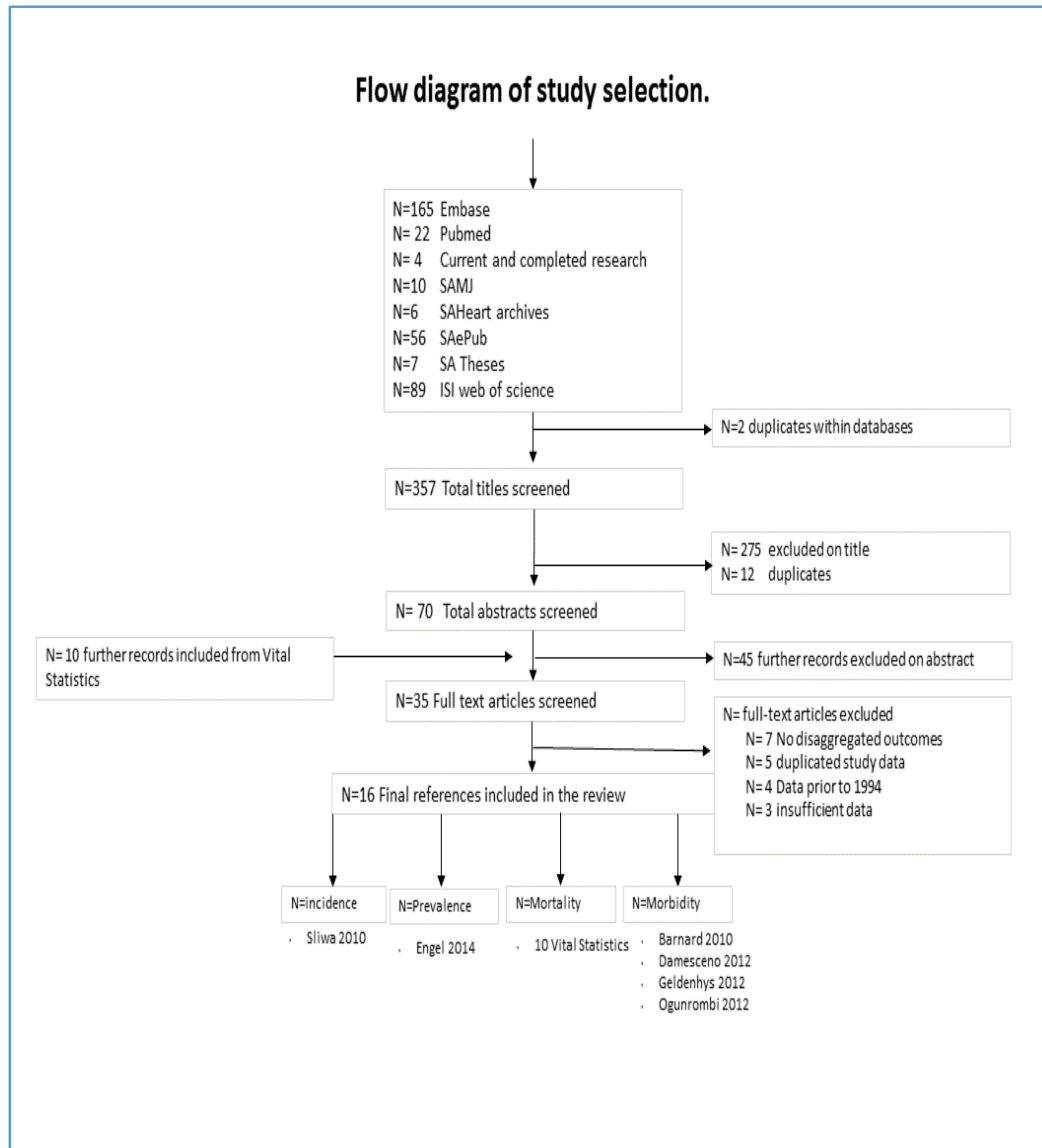


Figure 3.1. Flow diagram of study selection



Table 3.1. Excluded studies

	<b>First author</b>	<b>Year</b>	<b>Location (Hospital)</b>	<b>Reason for exclusion</b>
1	Skudicky	1994	Johannesburg (CHB)	Patients recruited prior to 1994
2	Van der Merwe	1994	Cape Town	Patients recruited prior to 1994
3	Skoularigis	1994	Johannesburg (CHB)	Patients recruited in the 1980s
4	Makhobo	1995	Ga-Rankuwa	Patients recruited prior to 1994
5	Kontozis	1998	Johannesburg (CHB)	Incomplete data
6	Van Oppell	2001	Cape Town (GSH)	No disaggregated data outcomes
7	Middlemost	2003	Port Elizabeth	No disaggregated data outcomes
8	Koegelenberg	2003	Cape Town (TBH)	No disaggregated data outcomes.
9	Williams	2006	Port Elizabeth	No disaggregated data outcomes
10	Sliwa	2008	Johannesburg (CHB)	Duplicate data, recent data included
11	Damasceno	2008	Multiple	Duplicate data, recent data included
12	Farooq	2008	Johannesburg (CHB)	Incomplete data
13	Sliwa	2009	Johannesburg (CHB)	Duplicate data, recent data included
14	Sliwa	2009	Johannesburg (CHB)	No disaggregated data outcomes
15	Geldenhuys	2011	Cape Town (GSH)	Duplicate data, recent data included
16	Koshy	2011	Cape Town (GSH)	Duplicate data, recent data included
17	Smit	2012	South Africa	Incomplete data
18	Chin	2012	Multiple	No disaggregated data outcomes
19	Oldgren	2014	Multiple	No disaggregated data available

*Acronyms: CHB – Chris Hani Baragwanath Hospital; GSH – Groote Schuur Hospital; TBH – Tygerberg Hospital.*

Table 3.2. Included studies

First author	Study type	Representativeness of cases to the general population with RHD	Completeness of dataset, including follow-up	Validity of case definitions and methods of ascertainment	Appropriateness of the study design to the research question	Overall assessment of quality – rated out of 16.
Sliwa	Hospital-based study accounting for catchment area	4	3	4	4	15
Engel	School-based study	4	4	4	4	16
Barnard	Hospital-related events	3	3	3	3	12
Damasceno	Hospital-related events	3	3	4	3	13
Geldenhuys	Hospital-related events	3	4	4	4	15
Ogunrombi	Hospital-related events	3	2	4	3	12
Statistics South Africa	Population-based study	3	3	2	4	12
Statistics South Africa	Population-based study	3	3	2	4	12
Statistics South Africa	Population-based study	3	3	2	4	12
Statistics South Africa	Population-based study	3	3	2	4	12
Statistics South Africa	Population-based study	3	3	2	4	12
Statistics South Africa	Population-based study	3	3	2	4	12
Statistics South Africa	Population-based study	3	3	2	4	12
Statistics South Africa	Population-based study	3	3	2	4	12
Statistics South Africa	Population-based study	3	3	2	4	12
Statistics South Africa	Population-based study	3	3	2	4	12
Statistics South Africa	Population-based study	3	3	2	4	12

Table 3.3. Characteristics of included studies

First author	Year	Location (Hospital)	No. of subjects	Study duration	Outcome(s) of interest	Risk of bias score <sup>†</sup>
Sliwa	2010	Johannesburg (CHB)	344	3 years	RHD incidence and others*	9 of 11
Engel	2012	Cape Town	2,720	4 years	RHD prevalence	6 of 6
Barnard	2010	Cape Town (TBH)	160	4 years	Surgical outcomes	6 of 9
Ogunrombi	2011	Cape Town (GSH)	770**	16 years	Surgical outcomes	5 of 8
Geldenhuys	2012	Cape Town (GSH)	138	10 years	Surgical outcomes	12 of 12
Damasceno	2012	Multiple***	40***	3 years	HF attributable fraction,	5 of 9
Statistics South Africa	2005	South Africa	2,433,051	6 years	RHD mortality	3 of 6
Statistics South Africa	2006	South Africa	1,120,313	2 years	RHD mortality	3 of 6
Statistics South Africa	2007	South Africa	591,213	1 year	RHD mortality	3 of 6
Statistics South Africa	2008	South Africa	607,184	1 year	RHD mortality	3 of 6
Statistics South Africa	2009	South Africa	601,113	1 year	RHD mortality	3 of 6
Statistics South Africa	2010	South Africa	592,073	1 year	RHD mortality	3 of 6
Statistics South Africa	2011	South Africa	572,673	1 year	RHD mortality	3 of 6
Statistics South Africa	2012	South Africa	543,856	1 year	RHD mortality	3 of 6
Statistics South Africa	2013	South Africa	505,803	1 year	RHD mortality	3 of 6
Statistics South Africa	2014	South Africa	480,476	1 year	RHD mortality	3 of 6

*Acronyms: CHB – Chris Hani Baragwanath Hospital; GSH – Groote Schuur Hospital; HF –heart failure; IE – infective endocarditis; RHD – Rheumatic Heart Disease; TBH – Tygerberg Hospital.*

\* Study also reports prevalence of atrial fibrillation, prevalence of heart failure, incidence of infective endocarditis, and incidence of surgery

\*\* Original study included additional participants; only this subset is analysed for the outcome(s) of interest

\*\*\* Sites include Cape Town (n=50) and Johannesburg (n=82); in total, 40 South African patients with RHD are included in the study

† Total possible score reflects the number of parameters in the respective studies able to be evaluated; the higher the score, the lower the risk of bias.

Table 3.4. Characteristics of included surgical studies

First author, year published	Barnard, 2010	Geldenhuys, 2012	Ogunrombi, 2012*
Method of recruitment	Consecutive isolated mitral valve replacements	Primary single mitral valve procedures	All primary valve procedures (aortic and mitral valves)
Study exposure	Isolated mitral valve replacements	69 Mitral valve repairs and 69 mitral valve replacements, matched	First incidence, single aortic and mitral valve repair and replacement
No. of participants	187	138	770
Study duration	5 years (1998-2002)	10 years (2000-2010)	16 years (1993-2008)
Mean follow-up	5.41 years	4.4±3.0 years	n/s
Lost to follow-up	28.3%	0%	n/s

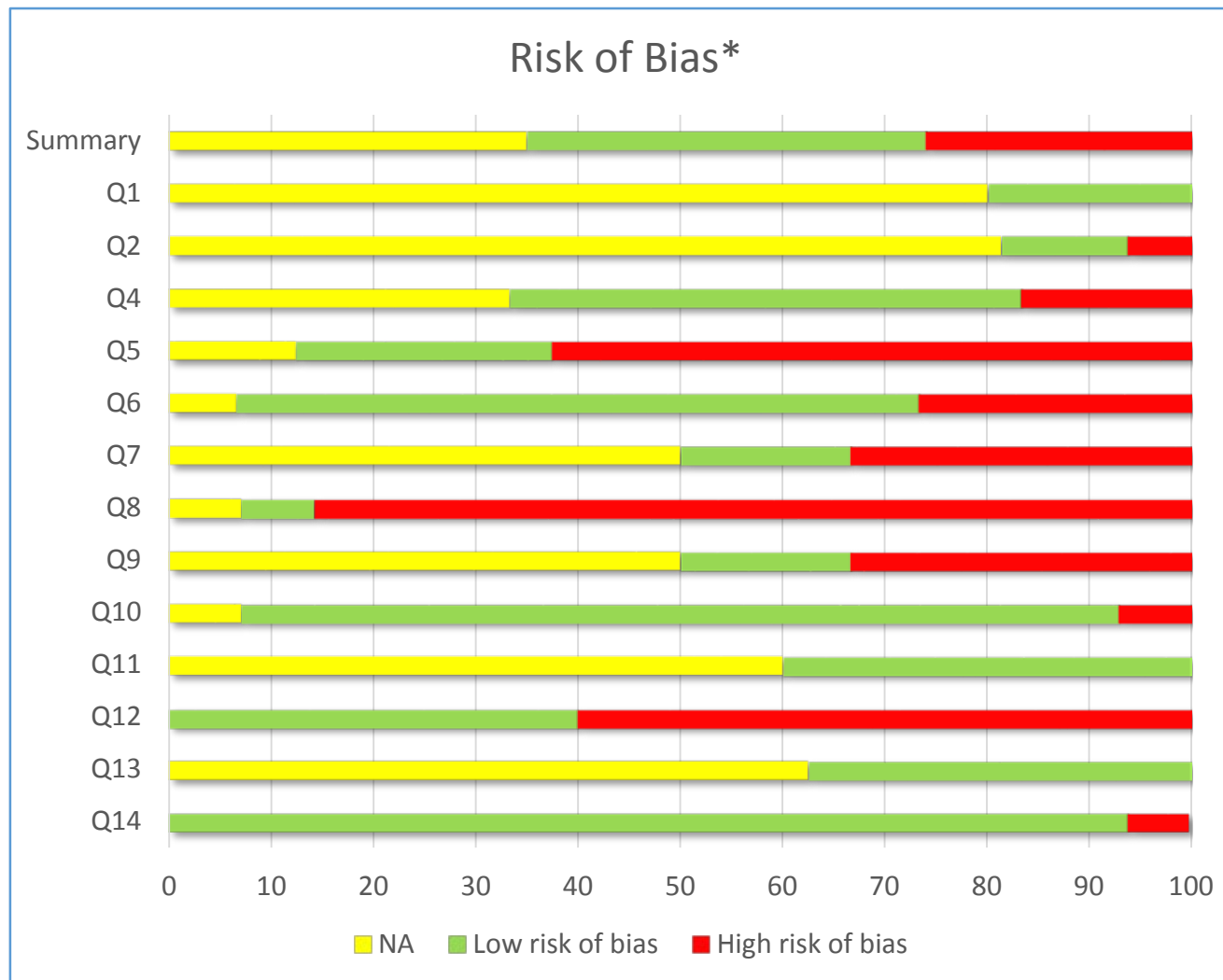
*\*Original study included additional participants; only this subset are analysed for the outcome(s) of interest.*

*Methodological assessment of included studies*

All studies were classified as being of high quality (Table 3.3). We present the characteristics and risk of bias assessment of included studies in Table 3.3. The overall assessment score for risk of bias ranged from 50% (3/6) to 100% (6/6 or 12/12). The lower score indicates the higher risk of bias assessment. The overall risk of bias of all the included studies was low. Figures 3.2 and 3.3 depict the study-specific and question-specific scores for risk of bias respectively. Red- high risk of bias, yellow-medium risk and green-low risk of bias.

		Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14
Statistics South Africa	2005		●			●	●		●		●	●	●	●	●
Statistics South Africa	2006		●			●	●		●		●	●	●	●	●
Statistics South Africa	2007		●			●	●		●		●	●	●	●	●
Statistics South Africa	2008		●			●	●		●		●	●	●	●	●
Statistics South Africa	2009		●			●	●		●		●	●	●	●	●
Barnard	2010	●	●		●	●	●	●	●	●	●	●	●	●	●
Sliwa	2010		●			●	●				●	●	●	●	●
Statistics South Africa	2010		●			●	●		●		●	●	●	●	●
Ogunrombi	2011	●	●		●	●	●	●	●	●	●	●	●	●	●
Statistics South Africa	2011		●			●	●		●		●	●	●	●	●
Engel	2012		●		●	●	●	●		●	●	●	●	●	●
Geldenhuys	2012	●	●		●	●	●	●	●	●	●	●	●	●	●
Statistics South Africa	2012		●			●	●		●		●	●	●	●	●
Damasceno	2012	●	●		●	●	●	●	●	●	●			●	●
Statistics South Africa	2013		●			●	●		●		●	●	●	●	●

Figure 3.2. Study-specific risk of bias scores



\*Question three pertained to randomised-controlled trials and therefore was not included in the assessment.

Figure 3.3. Risk of bias

### 3.5 Results

#### *Incidence*

There were 344 newly diagnosed cases of RHD from a single prospective study (Sliwa et al., 2010). Our secondary analysis of the published data using the age-specific incidence rates computed an overall crude incidence estimate of 24.7 per 100,000 population per annum amongst patients older than 13 years. The tabulated crude age-specific incidence estimates per 100,000 persons are presented in age strata in Table 3.4, together with 95% confidence intervals. We computed for the first time the underlying population estimates using the reported age-specific incidence rates.

Table 3.4. Incidence per 100,000 population per age stratum

Age category (years)	Number of cases	Incidence per 100,000	95% Confidence intervals <sup>†</sup>	Calculated population <sup>‡</sup>
14-19	10	30	[14.4-55.2]	333,333.3
20-29	56	15	[11.3-19.5]	373,333.3
30-39	84	17	[13.6-21.1]	494,117.6
40-49	59	31	[23.7-40.0]	190,322.6
50-59	65	38	[29.3-48.4]	171,052.6
60 +	70	53	[41.3-67.0]	132,075.5
Total	344	24.7	[22.1-27.4]	1,394,235.0

<sup>†</sup> 95% CIs were computed using the "CI" routine in STATA; <sup>‡</sup> Population was calculated as follows: 100,000 X (Number of cases/Incidence per 10<sup>5</sup>)

#### *Prevalence*

A single study reported on prevalence (Engel, 2012) with revised data using the WHF criteria (Engel et al., 2015). Of the 2,720 children examined, 1,604 (58.9%) were female, with the mean age of 12.2±4.2 years (Table 3.5). Overall, echocardiographic screening identified 55 children showing evidence of RHD, corresponding to a prevalence of 20.2 cases per 1,000 children (95% CI 15.3 to 26.2). Of the 55 children with RHD, 13 (23.6%) had definite and 42 (76.4%) had borderline RHD. The prevalence of definite and borderline RHD was 4.8 cases per 1,000 children (95% CI 2.5 to 8.1) and 15.4 cases per 1,000 children (95% CI 11.1 to 20.8) respectively.

*Acute heart failure and rheumatic heart disease*

The demographic findings as well as the clinical outcomes of South African patients included in THESUS-HF with a primary diagnosis of RHD are described in Table 3.6 (Damasceno et al., 2012). The mean age was  $43.6 \pm 14.8$  years, median age 43 years [IQR 32-55] and 18 (45%) of the patients were female. The mean initial hospitalisation stay was  $16.6 \text{ days} \pm 26.3$  with an initial hospitalisation mortality of 17.5% [95% CI, 4.3 to 32.8] (n=7). The 60-day mortality was 24.8% (95% CI, 13.6 to 42.5) (n=9) and 180-day mortality was 35.4% (95% CI, 21.6 to 54.4) (n=12)].

Table 3.5 Demographics and mortality of rheumatic heart disease patients admitted for acute heart failure

Outcomes after admission for acute heart failure		N	%	95% C.I.
Demographic characteristics				
	Participants, N	40		
	Female, N (%)	18	45	
	Age			
	Mean (SD)	43.6 (14.8)		
	Median (IQR)	43 (32-55)		
Length of initial hospital stay, days				
	Mean (SD)	16.6 (26.3)		
	Median (IQR)	7 (4-13.5)		
Initial hospitalisation mortality, N (%)		7	17.5	
Readmission to day 60, N (%) [95% C.I.]		3	11.5	[13.6-42.5]
Death to day 60 N (%) [95% C.I.]		9	24.8	[13.6-42.5]
Death or readmission to day 60 N (%) [95% C.I.]		10	27.9	[16.0-46.0]
Death to day 180 N (%) [95% C.I.]		12	35.4	[21.6-54.4]

Acronyms: CI – Confidence interval; IQR – Interquartile range; N – number; SD – Standard deviation.

*Newly diagnosed rheumatic heart disease*

Sliwa et al. (Sliwa et al., 2010) documented the findings at presentation and mid-term outcome of newly diagnosed RHD patients. At presentation, 247 (72%) of cases were on at least one form of cardiac medication. AF was present in 34 (10%) and impaired systolic function was found in 51 (15.4%) of the 330 where this was recorded. After a 30-month follow-up period, 20 patients (5.8%) were treated



for infective endocarditis based on the Duke criteria and 75 (21.8%) were subjected to either valve repair or replacement.

#### *Perioperative outcomes*

Table 3.7 describes mortality in surgical patients. In the study from Barnard et al, reviewing outcomes of primary mitral valve replacements, there were nine early deaths (to 30 days) (4.81%) and 23 (12.3%) late deaths (after 30 days) of the 187 patients enrolled. The denominator was adjusted to include 27 patients with incomplete data who were originally excluded from the analysis (Barnard et al., 2010). Geldenhuys reported a 0.7% 30-day mortality (n=1)(Geldenhuys et al., 2012) while Ogunrombi reports a 2% 30-day mortality (n=15) (Ogunrombi, 2011). These studies reported outcomes following mitral valve replacements and repairs in a propensity-matched cohort (Geldenhuys) and valve surgery (valve replacements or repairs) in a cohort of rheumatic and non-rheumatic patients (Ogunrombi). Freedom from all-cause mortality at 5-years was 74.6% in Barnard's study and  $96 \pm 4$  % for valve repairs and  $90 \pm 4$  % for valve replacements respectively in the Geldenhuys study. Geldenhuys had complete 10-year follow-up and reported a  $96 \pm 3$  % 10-year survival from all-cause mortality in the repair group and  $80 \pm 11$  % in the replacement group with a  $70 \pm 8$  % survival from valve-related mortality in the repair group compared to  $69 \pm 11$  % in the replacement group.

#### *Sequelae at presentation and post-surgical outcomes*

Table 3.7 also details additional findings at presentation and clinical outcomes following surgery. Of 187 patients, 61 (32.5%) were in atrial fibrillation (AF) prior to mitral valve replacement, as were 38 (49.3%) of those undergoing either mitral valve repair or replacement in the Geldenhuys cohort (Figure 3.5). Nine (6.52%) developed new-onset AF post-surgical intervention.

First author, year published		Barnard, 2010	Geldenhuys, 2012	Ogunrombi, 2012
Number of participants		187	138	770
30-day mortality		9 (4.81%)	1 (0.72%)	15 (2%)
Mortality beyond 60 days		23 (12.3%)	14 (10.1%)	n/s
Valve-related mortality		12(6.4%)	7 (5.1%)	n/s
Freedom from all-cause mortality				
	5 years	140 (74.9%)	96±4% repair, 90±4% replacements	n/s
	10 years	n/s	91±4% repair, 74±11% replacements	n/s
Freedom from valve-related deaths				
	5 Years	134 (71.6%)	96±3% repair, 92±4% replacements	n/s
	10 Years	n/s	96±3% repair, 80±11% replacements	n/s
Freedom from valve-related events (deaths, reoperations and morbidity)				
	5 Years	n/s	80±6% repair, 86±5% replacements	n/s
	10 Years	n/s	70±8% repairs, 69±11% replacements	n/s
Atrial Fibrillation	Pre-operative	61/187 (32.5%)	68/138 (49.3%)	n/s
	New onset	n/s	9/138 (6.52%)	n/s
Stroke		1.61%/yr.	2/138 (1.44%)	n/s
Systemic Embolism		1.61%/yr.	n/s	n/s
Prosthetic valve thrombosis		0.8%/yr.	1/138 (0.72%)	n/s
Bleeding		1.27%/ yr.	4/138 (2.9%)	n/s
Infective endocarditis		0.57% /yr.	4/138 (2.9%)	n/s

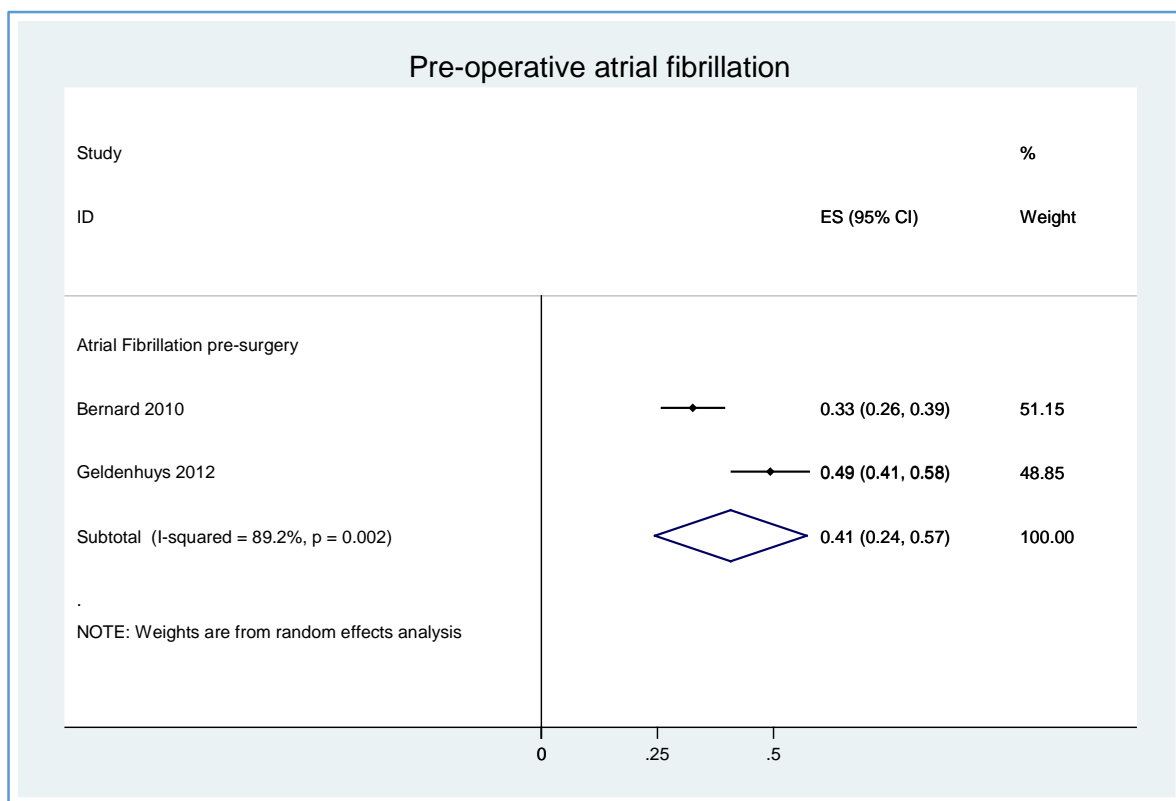
Acronym:Yr, year

Table 3.6 Fatal and non-fatal outcomes in surgical reviews

The data were not amenable to meta-analyses for most outcomes, except for pre-operative AF and 30-day mortality, given that for most outcomes, only a single study contributed data.

### *Pre-operative atrial fibrillation*

Two studies (n = 325 participants) contributed to a combined prevalence for pre-operative atrial fibrillation of 41% [95% CI, 24-57;  $I^2$ , 89.2%) as depicted in Figure 3.4.

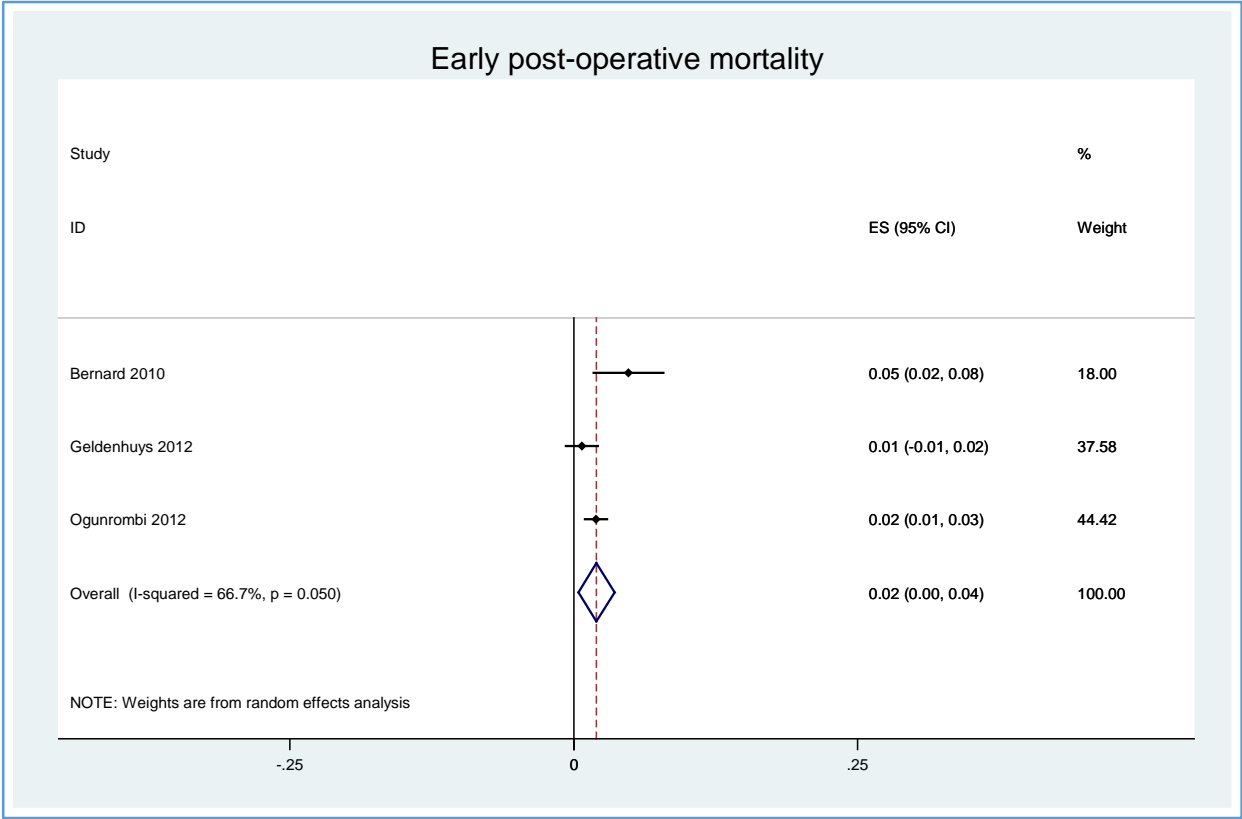


Acronyms: CI – Confidence interval; ES – Effect size.

Figure 3.4. Pre-operative atrial fibrillation

### *Post-operative mortality*

Of the 10 outcomes listed in Table 3.7, only early mortality (30-days) was amenable to meta-analysis, for which the combined prevalence was 2% [95% CI, 0 to 4;  $I^2$ , 66.7%], (three studies, 1089 participants) as shown in Figure 3.6. For the remaining outcomes, prevalence ranged from 1% (10-year stroke, heart failure at 5 and 10 years), 3% (prosthetic valve thrombosis at 5 and 10 years), 5% (10-year valve-related mortality), 6% (5-year valve-related mortality) and 25% (5-year all-cause mortality).



Acronyms: CI – Confidence interval; ES – Effect size.

Figure 3.5. Early post-operative mortality

In the remainder of the studies, a statistical synthesis of the data was not appropriate as there were only single estimates of each outcome of interest. We thus provide a narrative assessment. In patients with admissions for acute heart failure and an underlying diagnosis of RHD, the prevalence for death to day 60 was 22% and for death to day 180 was 33%.

There were only single variables reported in the outcomes of interest for both newly diagnosed RHD and post-operative RHD, these were therefore not suitable for meta-analysis. In the former, prevalence of outcomes ranged from 5.8% for confirmed infective endocarditis and 21.8% of requiring subsequent surgical intervention over the period of 30 months. In the post-operative studies, there were only single contributions to the outcomes of interest. Prevalence ranged from 1% (prosthetic valve thrombosis and stroke after 10 years), 3% (bleeding and infective endocarditis after 10 years) and 7% (atrial fibrillation (after 10 years)).

*Mortality*

The mortality rate attributed to RHD decreased from 1.27 (95% CI 1.17 to 1.39) in 1997 to 0.7 (95% CI 0.63 to 0.78) in 2012 as summarised in Table 3.8 and Figure 3.4. Data are as yet, not available for 2013-2014.

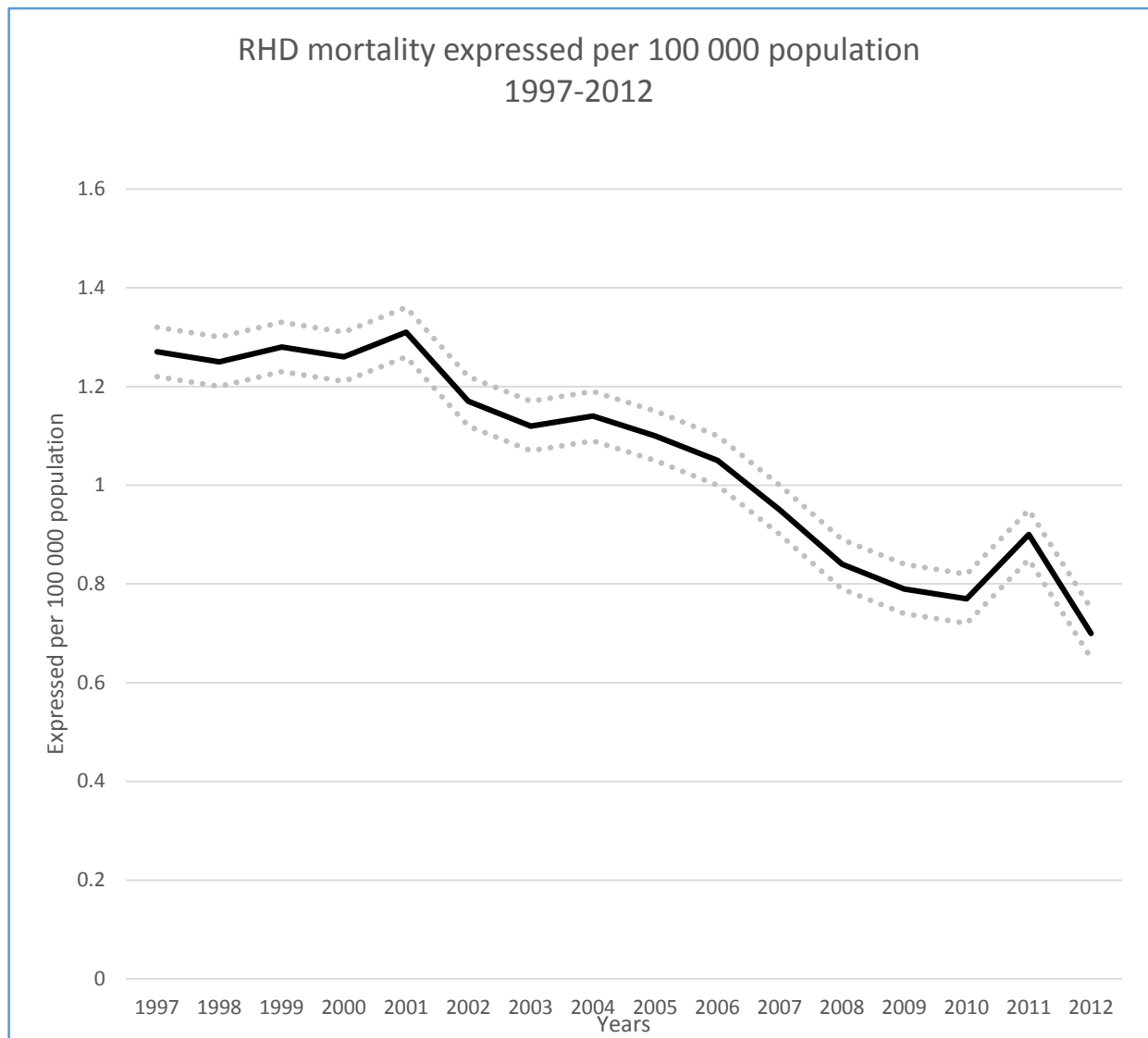
Table 3.7. Summary of Statistics South Africa reports

Year	Total deaths	RHD deaths	Proportion of deaths (%)*	Mid-year population**	RHD mortality per 100,000 95% CI <sup>#</sup>
1997	318,287	533	0.17	41,835,000	1.27 [1.17-1.39]
1998	367,689	525	0.14	42,130,500	1.25 [1.14-1.36]
1999	381,902	551	0.14	43,054,306	1.28 [1.18-1.39]
2000	413,969	551	0.13	43,685,699	1.26 [1.16-1.37]
2001	451,936	585	0.13	44,560,644	1.31 [1.21-1.42]
2002	499,268	532	0.11	45,454,211	1.17 [1.07-1.27]
2003	552,825	520	0.09	46,429,823	1.12 [1.03-1.22]
2004	567,488	532	0.09	46,586,607	1.14 [1.05-1.24]
2005	591,213	517	0.09	46,888,200	1.10 [1.01-1.2]
2006	607,184	496	0.08	47,390,900	1.05 [0.96-1.14]
2007	601,113	456	0.08	47,850,700	0.95 [0.87-1.04]
2008	592,073	408	0.07	48,687,000	0.84 [0.75-0.92]
2009	572,673	390	0.07	49,320,500	0.79 [0.71-0.87]
2010	543,856	384	0.07	49,991,300	0.77 [0.69-0.85]
2011	505,803	454	0.09	50,586,757	0.90 [0.82-0.98]
2012	480,476	365	0.08	51,770,560	0.70[0.63-0.78]

Acronyms: CI – Confidence interval; RHD – Rheumatic heart disease.

\* Proportion of deaths were calculated as follows: RHD deaths/total deaths

\*\* Mid-year population was obtained from <http://www.statssa.gov.za/#RHD> mortality per 100,000 was calculated as follows: RHD deaths/Mid-year proportion \*100,000 † 95% Confidence intervals were computed using the “CI” routine in STATA



Acronym: RHD – Rheumatic heart disease. Dotted lines represent upper and lower 95% confidence intervals.

Figure 3.6. Rheumatic heart disease mortality rate, 1997-2012

### 3.6 Discussion

This systematic review of the contemporary burden and outcome of RHD in South Africa shows several key findings. Firstly, there is a high incidence and prevalence of symptomatic RHD in adults and asymptomatic RHD among schoolchildren, respectively. Secondly, acute heart failure due to RHD is associated with a high case fatality rate affecting a third of patients within a year of diagnosis. In contrast, patients with RHD have excellent perioperative mortality and morbidity over a period of 10 years. Furthermore, we show that cause-specific mortality rates have decreased over the past 13 years, despite the persisting high burden of disease. Finally, while non-fatal outcomes of the disease such as AF, infective endocarditis, stroke and prosthetic valve thrombosis are common in cross-sectional studies of patients with RHD, we found no prospective studies of the incidence of these sequelae.

The estimate of the incidence of RHD is based on a single study from Soweto and may not be generalizable to the local and national population for several reasons. Firstly, although this study sought to report incident cases of RHD with heart failure, several patients were already on cardiac medication, pointing to likely chronicity of their illness. Secondly, the size of the population of Soweto may have been underestimated in the original report. According to the City of Johannesburg report, there were 1.4 million people 14 years and older and a total population of 3 million rather than 1 million at the time of the study (2006-2008) (City of Johannesburg Metropolitan Municipality, 2011). Thirdly, the follow-up period of the Soweto study was limited to 30 months, and it reported a limited number of outcomes (i.e., infective endocarditis and need for valve surgery). Finally, the catchment area of Chris Hani Baragwanath Hospital goes beyond the borders of Soweto and the Gauteng province, thus increasing the uncertainty about the precision of the estimates of incidence of RHD derived from this study (Cilliers, 2014; Clur, 2006).

The estimate of the prevalence of RHD is similarly based on a single study that was conducted in peri-urban communities of Cape Town. This study was confined to schoolchildren in whom no symptomatic RHD was identified during initial screening. A study of the whole population is required to provide a reliable estimate of the burden of RHD in a community. Furthermore, the majority of South African live in deprived rural areas where the prevalence of RHD may be expected to be higher. In addition, the natural history of asymptomatic RHD and the contribution to symptomatic disease are unknown. There is thus a need for studies of the lifetime prevalence of RHD in the general population.

Socioeconomic deprivation, poor access to healthcare, overcrowding and lack of basic household amenities play key roles in the pathogenesis of RHD. As the socioeconomic status of South Africans improves, the incidence of RHD would be expected to fall. Cilliers recently reported a marked decline in numbers of children with ARF and RHD presenting to Chris Hani Baragwanath Hospital in Soweto (where the Heart of Soweto Study was performed) from 1993-2010 (Cilliers, 2014). These data may reflect an epidemiological transition of RHD that is characterized by a falling incidence of severe RHD in children, a persisting high burden of symptomatic adults, and large number of borderline cases in the community. The decline in RHD mortality over the period 1997 to 2012 is consistent with this hypothesis, reflecting both a decline in incidence and improved access to medical and surgical treatment for prevalent cases.

The surgical case series with the longest and most complete follow-up reports a freedom from all-cause mortality of  $91 \pm 4\%$  for valve repairs and  $74 \pm 11\%$  for valve replacements at ten years. This suggests that in the current era, the prognosis for post-surgical patients is excellent and has improved significantly compared to previous reports (Skoularigis, 1994), which showed low rates of post-surgical survival, especially in younger patients. Conversely, patients presenting with severe symptomatic disease, such as those in the THESUS-HF study, had a 60-day and 180-day mortality of 24.8 and 35.4% respectively. These mortality rates are substantially higher than the overall estimates for the cohort of 15.6 and 17.8% respectively (Damasceno et al., 2012). These data suggest that patients with heart failure should be considered for early surgery. Unfortunately, surgery for RHD is available for only a proportion of the population in Africa (Mocumbi, 2012).

We report, for the first time, a consistent decline in the numbers of registered deaths attributed to RHD in South Africa in the period 1997 to 2012 (Statistics South Africa, 2014b). This is occurring simultaneously with an increase in the population over the same period, from approximately 41.8 million in 1997 to 51.8 million in 2012. The proportion of deaths due to RHD has decreased from 0.17% in 1997 to 0.08% in 2012 and the mortality rate per 100 000 population has decreased from 1.27 in 1997 to 0.7 in 2012.

Our study has several limitations. We derived the cause-specific mortality rates from Statistics South Africa who do not provide age-specific mortality rates; thus, age-adjusted mortality rates were not calculated. South African death statistics reports contain sufficient errors to affect the accuracy of cause of death coding (Burger et al., 2007; Burger et al., 2012). A recent report suggests that cause-specific mortality reporting was particularly poor when coding for cardiovascular



disorders (Burger et al., 2012). Very little quantitative synthesis was possible as the data were either not amenable to meta-analysis or only measured in single reports. In addition, our meta-analyses had significant heterogeneity. For the pre-operative outcome, the heterogeneity is likely due to the variations in the context and surgical intervention performed in the two studies. In the second meta-analysis, heterogeneity was expected as a number of factors beside the pre-existing medical diagnosis affects 30-day mortality (Hammermeister et al., 1990; Thalji et al., 2014).

#### *Implications for practice*

Despite the limitations of the studies used in this review, the findings of this study have important clinical implications. Patients with acute heart failure due to RHD are at high risk of death, and require consideration for definitive therapy such as surgical intervention.

#### *Implications for research*

There is a need to establish the incidence, prevalence and temporal trends of RHD in South Africa through appropriately designed sentinel studies that will be generalizable to the whole population. The existence of the mandatory notification system for ARF and the proposed reporting of the first diagnosis of RHD provide the basis for the establishment of a national surveillance system for the disease. Furthermore, prospective studies of the outcome of RHD are required to provide contemporary information on the sequelae of the disease. Prospective long-term studies of symptomatic patients such as the Global RHD Registry (REMEDY) (Karthikeyan et al., 2012b) are required as a barometer for the achievement of the 25% mortality reduction by the year 2025 that has been mandated by the World Health Organization Non-communicable Disease Action Plan (Remenyi et al., 2013).

### **3.7 Conclusion**

A limited number of studies show that the incidence and prevalence of RHD remain high. Patients hospitalised with acute heart failure due to RHD have significant mortality and should be targeted for early surgical intervention. Furthermore, patients hospitalised with acute heart failure due to RHD have a high case fatality rate in the months following diagnosis. However, surgery for RHD is associated with excellent post-operative outcomes, and there is evidence of falling cause-specific mortality at a population level.

## 4 Study 2: The natural history of asymptomatic rheumatic heart disease

### 4.1 Abstract

#### *Introduction*

There is limited information on the natural history of asymptomatic rheumatic heart disease (RHD) detected by echocardiography in schoolchildren. We have conducted a 5-year prospective study of this question.

#### *Methods*

From January 2008 through March 2012, 2720 schoolchildren were selected at random from the Vanguard communities of Cape Town, South Africa and screened for echocardiographic features of RHD using the World Heart Federation criteria. Linear and multivariable regression was used to identify independent predictors of progression, persistence or regression at follow-up.

#### *Results*

Thirteen definite and 42 borderline cases of RHD (n=55) were identified at initial diagnosis. Forty-four cases (80%; mean age  $13.8 \pm 4.0$  years; 29 (65.9%) female) were available for echocardiographic examination at a median follow-up of 60.8 months (interquartile range 51.3-63.5). Cases of definite RHD (n=10) either remained unchanged (n=7, 70%) or improved to a borderline status (n=3, 30%). Two definite RHD cases (20%) developed symptomatic disease. There were three outcomes of borderline RHD (n=34): (a) regression to normal (n=12, 35.2%), (b) persistent borderline state (n=15, 44.1%), and (c) progression to definite RHD (n=7, 20.6%). Pathological mitral regurgitation (MR) at initial diagnosis predicted persistent lesions at follow-up (hazard ratio 9.0, 95% confidence interval (CI) 1.9 to 41.7,  $P=0.005$ ) and had an area under the receiver-operating characteristic curve of 0.75 (95% CI 60.1 to 89.9), for the outcome of stable or worsening RHD.

#### *Conclusion*

There is a difference between the natural history of borderline compared to definite echocardiographic RHD in asymptomatic schoolchildren. One third of borderline RHD cases revert to normal, whereas definite RHD is associated with persistent or worsening disease over five years.

## 4.2 Introduction

There is a persistently heavy burden of rheumatic heart disease (RHD) in many developing countries and in some indigenous communities of developed countries (Milne et al., 2012b; Zühlke et al., 2014a). RHD exacts the highest number of disability-adjusted life-years of all cardiovascular diseases among 10–14-year-olds (516·6 per 100 000 people, 95% CI 425·3–647·0) and the second highest number among children aged 5–9 years (362·0 per 100 000 people, 294·6–462·0) (Murray et al., 2012b). There is increasing recognition of the entity of asymptomatic or latent RHD, which refers to individuals with echocardiographic evidence of RHD who have no known history of acute rheumatic fever (ARF) and no clinical symptoms (Beaton et al., 2014b). The pooled prevalence of asymptomatic RHD of 12.6 per 1000 children and adolescents living in endemic countries (Rothenbühler et al., 2014). However, the natural history of asymptomatic RHD that has been identified through active echocardiographic surveillance studies is not well defined (Mayosi, 2014).

There are several problems with the limited number of studies of the natural history of asymptomatic RHD detected by screening echocardiography (Beaton et al., 2014b; Bhaya et al., 2011; Paar et al., 2010; Saxena et al., 2011). Firstly, these studies have had relatively short follow-up periods ranging from 6 months to 2 years. The natural history of asymptomatic RHD beyond this period is unknown. Secondly, non-standardised criteria for the diagnosis of RHD have been used in three of the four studies of this question to date, (Bhaya et al., 2011; Paar et al., 2010; Saxena et al., 2011) which are associated with widely varying estimates of the prevalence of the disease even in the same study (Zühlke and Mayosi, 2013). The World Heart Federation (WHF) has developed evidence-based criteria for the echocardiographic diagnosis of RHD that serve as the new standard for research in this field (Remenyi et al., 2012a). Finally, these studies have had variable use of penicillin prophylaxis in patients with asymptomatic RHD which may affect the natural history of the condition.

We have used the WHF criteria for the echocardiographic diagnosis of RHD to assess the natural history of asymptomatic RHD disease in schoolchildren over five years.

### 4.3 Methods

These have been described in detail in Section 2.4. In summary, 78 learners with definite and probable RHD were identified during a school screening programme conducted between 2009 and 2012. These were diagnosed using published criteria (Zühlke, 2009). Subsequent to the publication of the World Heart Federation (WHF) criteria, these were reclassified using the updated criteria (Remenyi et al., 2012a).

Table 4.1. Classification of abnormal echocardiograms at enrolment

	<b>Classification by modified National Institutes of Health criteria</b>		<b>Classification by World Heart Federation criteria</b>
	Cases		Cases
Definite RHD	16	Definite RHD	13
Probable RHD	62	Borderline RHD	42
Total RHD	78	Total RHD	55

*Acronyms: RHD – Rheumatic heart disease*

Fifty-five learners with definite and borderline disease were identified (Table 4.1). These learners underwent a comprehensive clinical examination and repeat echocardiography. The dates of the original echocardiogram were noted, as well as the findings on repeat testing using the WHF criteria. The demographic details for each participant, including age, new contact details and medical status, were captured. Finally, the findings were reviewed, to identify persistors (category unchanged), progressors (category worsened – borderline to definite) and regressors (category improved – definite to borderline or borderline/definite to normal).

### 4.4 Results

#### *Participants*

The echocardiographic surveillance study identified 16, 62, and 344 schoolchildren with definite RHD, probable RHD, and possible RHD, respectively, by means of the modified NIH criteria. When the standardized WHF criteria for the diagnosis of asymptomatic RHD became available

during the course of the study, it was applied to the abnormal baseline surveillance echocardiograms which were re-classified into definite RHD or borderline RHD (Table 4.1). There were 13 schoolchildren with definite RHD and 42 with borderline RHD by WHF criteria at baseline echocardiography who were invited for the follow-up examination (n=55). Forty-four (80%) schoolchildren returned for a repeat visit. Table 4.2 shows the age, gender and follow-up duration of the 44 schoolchildren. Only two of the 10 schoolchildren with definite RHD at the enrolment visit were on secondary antibiotic prophylaxis at the time of follow-up, both over 85% of doses. There were 11 learners who were not reviewed for the following reasons: nine (16%) were not contactable, one (2%) was resident outside of South Africa and one (2%) refused to return for follow-up.

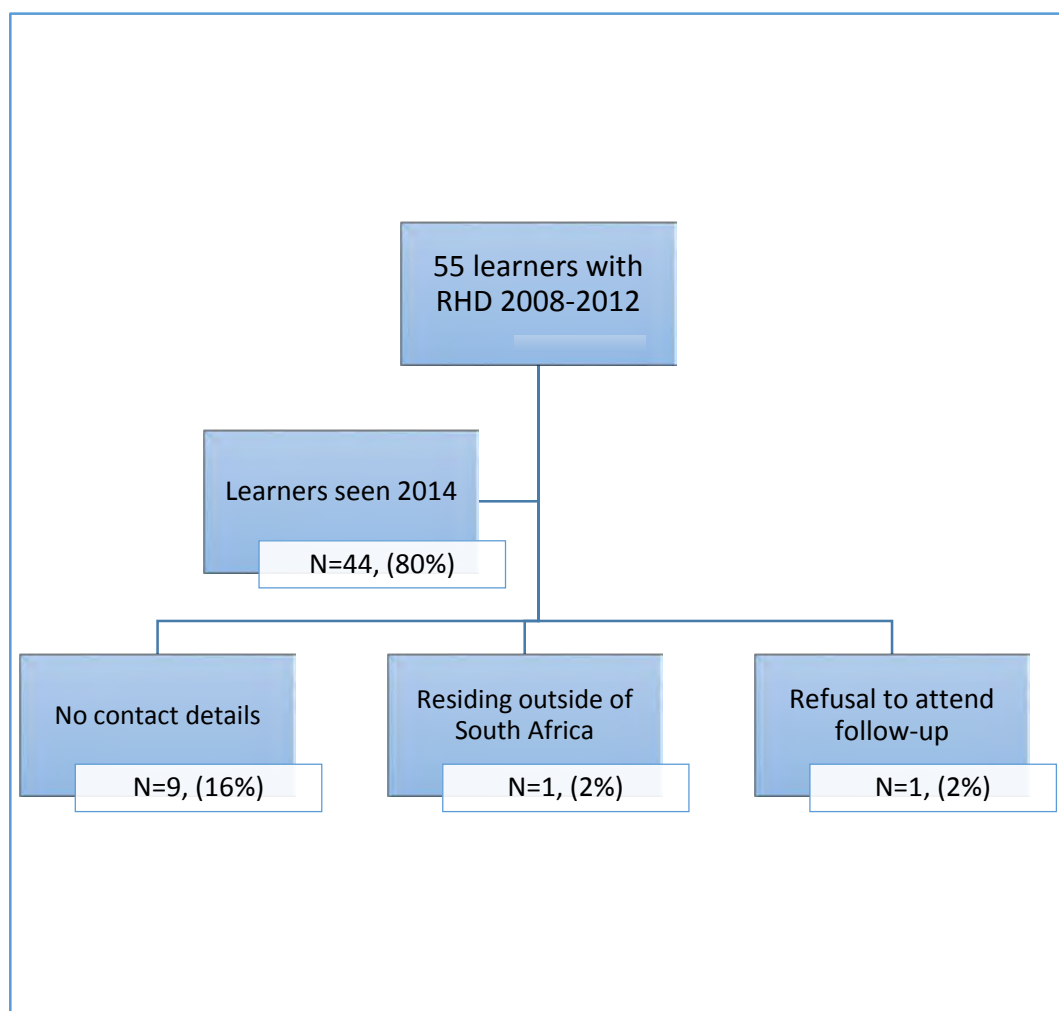


Figure 4.1. Percentage of follow-up

Table 4.2. Characteristics of the learners at follow-up visit

Characteristics	Cape Town, South Africa (N=44)
Mean age in years [SD] at initial diagnosis	13.8 [4.0]
Median age in years [IQR] (min, max) at initial diagnosis	13 [11-17] (5, 21)
Female sex – n (%)	29 (65.9)
Duration of follow-up, median months [IQR]	60.8 [51.3-63.5]
Changes in diagnosis of RHD in all participants	
Regressors (improved) n (%)	15 (34.1)
Persistors (remained the same) n (%)	22 (50)
Progressors (lesions worsened) n (%)	7 (15.9)
Ratio of persistors and progressors to regressors	2.06:1

Acronyms: *IQR* – Interquartile range; *max* – maximum; *min* – minimum; *SD* – Standard deviation.

### *Natural history*

Asymptomatic RHD was a dynamic phenotype characterized by progression, persistence or regression (Figure 4.2). There were different patterns of change in those with definite RHD compared to those with borderline RHD. Cases of definite RHD (n 10, 22.7%) either remained unchanged (n 7, 70%) or improved to a borderline status (n 3, 30%). There were three outcomes of borderline RHD (n 34, 77.3%): (a) regression to normal (n 12, 35.2%), (b) persistent borderline state (n 15, 44.1%), and (c) progression to definite RHD (n 7, 20.6%).

In total, 15 learners (34.1%) improved over the follow-up period to either borderline RHD or to a normal status. Half of the schoolchildren (n=22) remained in the same WHF category while seven others (15.9%) worsened, progressing from borderline to definite RHD. The number of definite cases of RHD had increased from 10 cases at baseline to 14 cases at follow-up (40% increase). The number of borderline cases of RHD was reduced from 34 to 18 at follow-up, based on 12 who regressed to normal, and 7 who progressed to definite RHD (Figure 4.2).

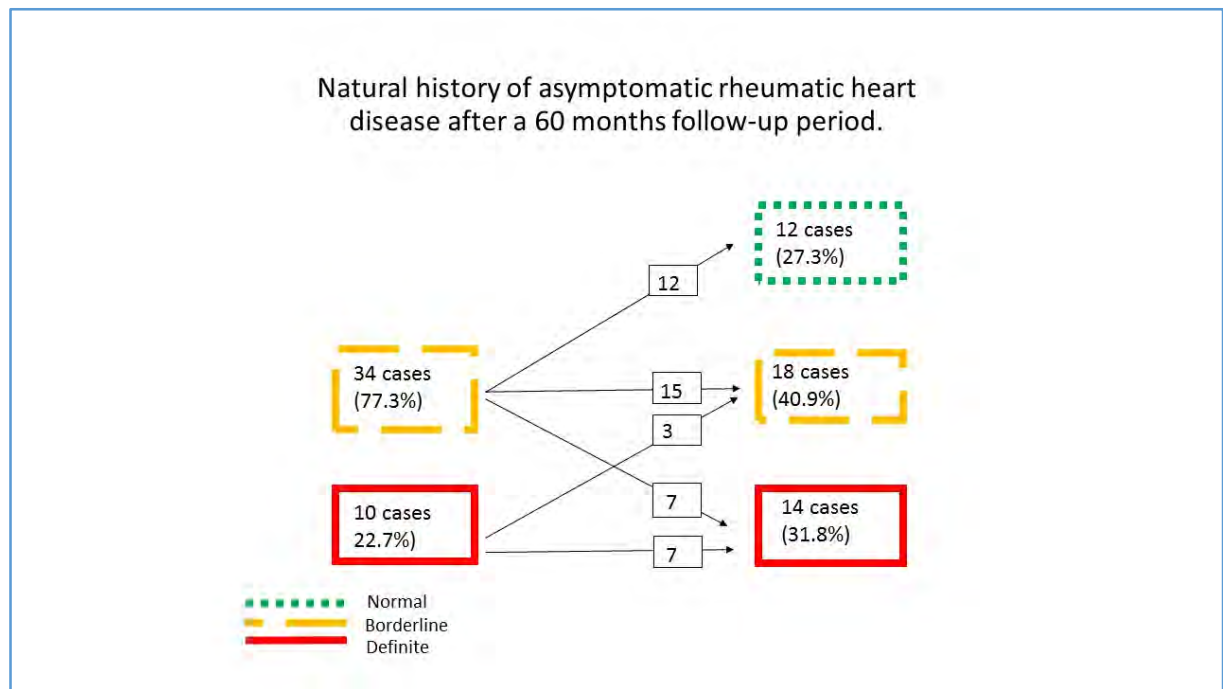


Figure 4.2. Natural history of asymptomatic rheumatic heart disease

These 14 cases of definite RHD displayed one of three patterns of valve disease: 12 cases (85.7%) had pathological MR with at least two abnormal morphological features of the mitral valve; one case (7.1%) had pathological AR with at least two abnormal features of the aortic valve; and one case (7.1%) had borderline disease of both aortic and mitral valves. There were no cases of mitral stenosis.

The 18 borderline cases had two patterns of valve involvement: either pathological MR (13 cases, 72.2%) or at least two morphological abnormalities of the mitral valve (5 cases, 27.8%). There were no cases of pathological AR or cases with two or more morphological features of the aortic valve.

#### *Factors to determine improvement or worsening of lesions*

In univariable analysis, cases with pathological MR were more likely to persist or progress over the follow-up period (OR 3.9, 95% CI 1.06 to 14.67,  $P=0.04$ ). Those with only pathological mitral valve morphology were more likely to regress over the follow-up period (OR 0.26, 95% CI 0.07 to 0.98,  $P=0.042$ ), Table 4.3. There was no significant association of age at diagnosis ( $P=0.582$ ), gender ( $P=0.617$ ) or residential area ( $P=0.929$ ) with outcome. In multivariable analysis, pathological MR at diagnosis remained the only significant predictor of persistent lesions (hazard ratio 9.0, 95% CI 1.9 to 41.7,  $P=0.005$ ) (Table 3). Pathological MR had an area under the receiver-

Study 2: The natural history of asymptomatic rheumatic heart disease operating characteristic curve of 0.75, 95% CI 60.1 to 89.9) for predicting the persistence of either definite RHD or borderline RHD.

Table 4.3. Echocardiographic features associated with progression or persistence of lesions

Echocardiographic features 2008	Regressors N=15(34.1)	Persistors and progressors N=29(65.9)	P	OR
Pathological mitral regurgitation n (%)	6(22.2)	21(77.8)	0.04	3.9[1.06-14.67]
Pathological aortic regurgitation n (%)	2(28.6)	5(71.4)	1	1.25[0.21-7.5]
Pathological mitral valve morphology n (%)	10(50)	10(50)	0.042	0.26[0.07-0.98]

Acronyms: N – number; OR – Odds ratio.

### *Symptomatic disease*

There were two cases that developed clinical symptoms of RHD over the five year period. Patient one was a 16-year-old girl first seen four years and three months earlier. Her original classification was that of definite RHD, with clinical pathological MR and two additional morphological features of the mitral valve on echocardiogram. Upon follow-up, she presented with fatigue, shortness of breath, a 3/6 pansystolic murmur on auscultation best heard at the apex at eight weeks of pregnancy. On echocardiography, she had pathological MR and three abnormal morphological features of the mitral valve with normal left ventricular function. She was commenced on diuretics and referred to a tertiary centre. She had been adherent to monthly benzathine penicillin and had no history of either sore throat or episodes of acute rheumatic fever (ARF).

The second patient was 22 years old, who was enrolled 5 years and 3 months prior to the follow-up visit. Her original classification was borderline RHD on the basis of pathological MR. She tested human immunodeficiency virus (HIV) positive prior to the follow-up visit but was non-adherent to anti-retroviral therapy. She had no history of sore throat or symptoms consistent with ARF. She was dyspnoeic on examination, had a gallop rhythm and pansystolic murmur, and a displaced apex. On echocardiography, she had severe MR with rheumatic morphological features, and an increased left ventricular end-diastolic diameter of 57 mm (Z score 2.55) and decreased left ventricular ejection fraction of 45%. She was subsequently lost to follow-up.



## 4.5 Discussion

There are three key findings of this study. Firstly, definite or borderline RHD in asymptomatic schoolchildren with no history of ARF is a dynamic phenotype which may regress to normal, remain unchanged, or progress to more severe and even symptomatic disease in significant proportions of affected individuals. In this study, one third of schoolchildren reverted to normal after 5 years of follow-up, with the rest either having persistent or worsening disease. Secondly, the natural history of definite RHD is different from that of borderline RHD. Whereas all cases that reverted to normal were in the borderline category, there is no case of definite RHD that regressed to a normal state. Therefore, the new WHF criteria appear to identify diagnostic categories of asymptomatic RHD that may have a varying prognosis. Finally, the presence of pathological MR is a strong predictor of persistence and deterioration of disease regardless of whether the diagnosis is definite or borderline RHD.

Our results are consistent with the findings of other investigators, suggesting that the observations may be generalizable to other populations. Previous natural history studies of asymptomatic RHD detected by echocardiography in patients without a previous history of ARF have reported the persistence of lesions in 53-68% of cases at about two years of follow-up, a proportion that is in line with our study (Figure 4.3) (Beaton et al., 2014b; Bhaya et al., 2011; Paar et al., 2010; Saxena et al., 2011). In addition, the predictive value of definite RHD and significant mitral valve disease for persistent or progressive disease has been found by others. Furthermore, our finding that isolated mitral valve morphological abnormalities were more likely to be associated with improvement or regression of lesions is consistent with observations in India (Bhaya et al., 2010). In contrast, other investigators have shown that an increased number of morphologic abnormalities are associated with persistence and progression of disease (Beaton et al., 2014b). It is possible that the determination of morphological abnormality on the heart valves is subject to greater observer variation, confounding by technical settings of echocardiography, and affected by the prevalence of other conditions such as endomyocardial fibrosis in the background population.

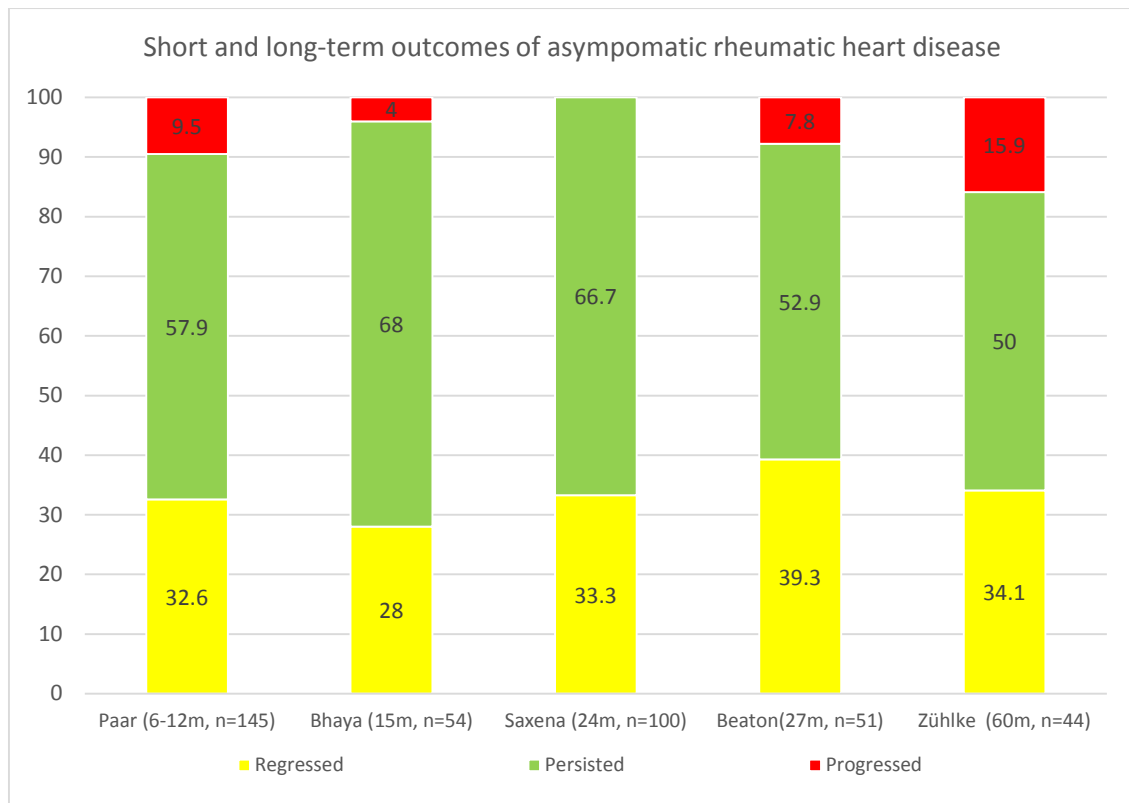


Figure 4.3. Reports of natural history of asymptomatic rheumatic heart disease

To the best of our knowledge, we report the first echocardiographic screening study of asymptomatic RHD with a five-year follow-up. Our study, however, has several limitations. Firstly, the sample size is small and therefore likely to be hypothesis generating rather than providing a definite answer to the question of the natural history of echocardiographic RHD in asymptomatic schoolchildren. Surveillance studies that are at least 10 times the size of this study will be required to address this question in a conclusive manner. Secondly, auscultation was not performed at the time of enrolment of the participants in this study. This decision was made on the basis of the superior performance of echocardiography in the detection of asymptomatic RHD (Marijon et al., 2007). Therefore, this is a study of asymptomatic RHD, which cannot address the question of the outcome of subclinical versus asymptomatic clinical RHD. Thirdly, subjects with definite RHD based on the modified NIH criteria were referred to local clinics for secondary antibiotic prophylaxis. The use of antibiotic prophylaxis against ARF may be expected to influence the natural history of asymptomatic RHD (WHO Technical Report Series, 2004). However, compliance with our recommendation was only confirmed in two out of the 16 schoolchildren who received this advice (one improved from her borderline status, and one was a definite case that deteriorated to a clinical case). Thus the use of antibiotic prophylaxis is unlikely to have affected the natural history of asymptomatic RHD in this study. Finally, the 20% loss to follow-up rate has led to incomplete ascertainment of outcomes at the end of the follow-up period in a significant proportion of cases.

However, the follow-up rate of 80% is comparable to other studies in this field (Beaton et al., 2014b; Bhaya et al., 2011; Paar et al., 2010; Saxena et al., 2011).

Our findings have important implications for clinical practice and research. A diagnosis of asymptomatic RHD on echocardiography requires confirmation in follow-up studies due to the dynamic nature of the condition – which may resolve, persist or deteriorate. A minimum period of follow-up of 5 years is required to identify those who develop episodes of ARF and symptomatic RHD and require management according to evidence-based standard guidelines (Beaton et al., 2014b; WHO Technical Report Series, 2004). However, the management of subclinical RHD is unknown (Zühlke and Mayosi, 2013). There is a need for a large randomised controlled trial of antibiotic prophylaxis to determine the efficacy and cost-effectiveness of secondary prevention in asymptomatic RHD (Mayosi, 2014; Zühlke and Mayosi, 2013).

## **4.6 Conclusion**

In this report, we present the natural history of asymptomatic RHD as defined by the WHF criteria. This is a dynamic condition that may regress, persist or progress to symptomatic disease over five years of follow-up. The presence of pathological MR is a strong predictor of persistent or progressive disease. Regular follow-up is required for a minimum period of five years, and studies are required to determine whether antibiotic prophylaxis is efficacious and cost-effective in preventing the progression of asymptomatic RHD to symptomatic disease.

## **5 Study 3: Alternate screening modalities of detecting rheumatic heart disease in asymptomatic school children**

### **5.1 Abstract**

#### *Introduction*

Echocardiography is the diagnostic test of choice for rheumatic heart disease (RHD). The utility of standard echocardiography for screening large numbers of subjects is limited by high cost, complex diagnostic protocols, and time to acquire multiple images. We evaluated the performance of a brief hand-held echocardiography protocol and computer-assisted auscultation in detecting asymptomatic RHD with or without pathological murmur.

#### *Methods*

Thirty-four asymptomatic schoolchildren with definite or borderline RHD based on World Heart Federation criteria and 64 healthy controls were examined by standard cardiac auscultation to detect pathological murmur. Hand-held echocardiography using a focused protocol which utilises one view (i.e., parasternal long-axis) and one measurement (i.e., mitral regurgitant jet) and computer-assisted auscultation utilising an automated decision tool were performed on all participants.

#### *Results*

The sensitivity of the computer-assisted auscultation to detect an abnormal murmur in cases of definite or borderline RHD was 3% (95% confidence intervals (CI) 0.7 to 15.3%) and specificity was 93.7% (95% CI 84.5 to 98.2%). The sensitivity of the focused hand-held echocardiography protocol to identify cases of definite or borderline RHD was 76.5% (95% CI 58.8 to 89.3%) with a specificity of 100%. The test reliability of echocardiography was 98.7% for detecting definite disease and 91.4% for detecting borderline disease with adjusted diagnostic odds ratios of 1562.5 and 241.7 for detecting definite and borderline disease, respectively.

#### *Conclusion*

Computer-assisted auscultation has a very low sensitivity but high specificity for pathological murmur in asymptomatic RHD. Focused hand-held echocardiography has moderate sensitivity but high specificity and diagnostic utility for definite or borderline RHD in asymptomatic schoolchildren.

## 5.2 Introduction

Recent surveillance studies from Africa, Asia, Australasia and Oceania have documented the high prevalence of asymptomatic rheumatic heart disease, i.e., asymptomatic rheumatic heart disease in the absence of a history of preceding acute rheumatic fever in schoolchildren (Rothenbuhler et al., 2014). These studies have also demonstrated the superiority of portable echocardiography over auscultation with the ordinary stethoscope in detecting the early structural and functional changes of rheumatic heart disease (Anabwani and Bonhoeffer, 1996; Ba-Saddik et al., 2011; Beaton et al., 2012; Bhaya et al., 2010; Carapetis et al., 2008; Grimaldi et al., 2012; Marijon et al., 2006; Marijon et al., 2007; Marijon et al., 2008; Paar et al., 2010; Roberts et al., 2013a; Saxena et al., 2011; Webb et al., 2011). The World Heart Federation (WHF) has developed evidence-based criteria for the echocardiographic diagnosis of rheumatic heart disease that serve as the new standard for research in this field (Remenyi et al., 2012b). However, portable echocardiography machines are expensive, and the screening protocols are complex, requiring highly-trained health professionals for acquisition and interpretation of the images (Mirabel et al., 2012b). Furthermore, the scanning protocol requires the acquisition of multiples images over a significant time period which limit the number of subjects that can be screened in field conditions. Therefore, there is a need to develop simple, affordable and reliable screening modalities and protocols for asymptomatic rheumatic heart disease in resource-poor settings (Zühlke and Mayosi, 2013).

Computer-assisted auscultation, a promising modality in screening for structural heart disease, uses a digital stethoscope combined with acoustic neural networking to provide a visual display of heart sounds and murmurs, analysing the recordings to distinguish between innocent and pathological murmurs (Zühlke et al., 2012a). Therefore, auscultation using a digital stethoscope together with an objective computer algorithm to identify pathological murmurs may improve the sensitivity and positive predictive value of cardiac auscultation. The performance of computer-assisted auscultation in the diagnosis of asymptomatic rheumatic heart disease is not known.

Hand-held echocardiography machines represent an important advancement over standard portable ultrasound equipment because of their small size and lower cost, but the lack of Doppler capabilities hampers the widespread use of these devices. Nevertheless, recent reports found that, compared to the use of portable echocardiography and full World Heart Federation criteria., hand-held portable echocardiography was sensitive and specific for the detection of asymptomatic RHD using modified WHF criteria (Beaton et al., 2014a). This protocol, however, requires the

acquisition of multiple images and expertise in recognising morphological features of rheumatic heart disease. We have therefore utilised a simple protocol called FOCUS (i.e., A FOCused method Utilizing hand-held echocardiography in Screening for RHD), which aims to identify one cardiac abnormality in the shortest possible time by a minimally trained observer for the diagnosis of rheumatic heart disease. We hypothesized that a simple protocol, using the single mitral regurgitation jet-length criterion of Mirabel et al (Mirabel et al., 2012b) with a hand-held echocardiogram may have high sensitivity and specificity in detecting rheumatic heart disease in asymptomatic schoolchildren.

The aim of this study was to assess the diagnostic utility (sensitivity, specificity, negative and positive predictive values, test efficiency and time) of computer-assisted cardiac auscultation and the focused protocol using hand-held echocardiography in the diagnosis of asymptomatic rheumatic heart disease in a population with a high burden of asymptomatic rheumatic heart disease. Computer-assisted auscultation was also compared to standard auscultation by a cardiologist for detection of pathological murmur.

### **5.3 Methods**

The methods used in this study are outlined in detail in Section 2.4 of this thesis.

### **5.4 Results**

#### *Characteristics of participants*

There were 34 subjects participants with either definite or borderline rheumatic heart disease, according to the World Heart Federation criteria for echocardiographic diagnosis of rheumatic heart disease who were recruited between August 2013 and September 2014. The mean age of these participants was 18.4 years ( $\pm 4.6$  years) and median age was 19 [IQR 16-23]; their minimum age was 8 years, their maximum age was 25 years, and 59.7% were female. There were 64 healthy controls with a mean age of 17.1 years ( $\pm 4.6$  years), median age 17 [IQR 15-21.5], minimum age 10 years, maximum age 25 years, and 68.5% were female.

*Performance of standard and computer-assisted auscultation and hand-held and portable echocardiography*

Six children had clinically detected murmurs of whom five were cases of asymptomatic rheumatic heart disease with a pathological murmur (5/34, 14.7%), and a single control participant with an innocent murmur (1/64, 1.6%). Computer-assisted auscultation detected one participant with an abnormal murmur, diagnosed as asymptomatic RHD (1/34, 2.9%). Twenty-six children (26/34, 76.5%) were identified as screen-positive using the focused hand-held echocardiography protocol (Table 5.1).

*Computer-assisted auscultation: Test characteristics*

The sensitivity of the automated auscultation decision to detect an abnormal murmur in cases of definite or borderline rheumatic heart disease was 3% (95% CI 0.7 to 15.3%). The specificity was 93.7% (95% CI 84.5 to 98.2%). The positive predictive value was 20% (95% CI 5-71.6%), while the negative predictive value was 64.1% (95% CI 53.4-73.8%). The adjusted likelihood ratios were 0.02 (positive likelihood ratio) and 0.56 (negative likelihood ratio) respectively, with a percentage of abnormal murmurs in cases of rheumatic heart disease equalling 61.9% and an adjusted diagnostic odds of 0.03 as shown in Table 5.1.

Table 5.1. Test characteristics for detecting subclinical rheumatic heart disease

<b>Performance characteristics</b>	<b>Computer-assisted auscultation</b>	<b>Hand-held echocardiography and FOCUS protocol</b>
Sensitivity	3% (0.7-15.3%)	76.5% (58.8-89.3%)
Specificity	93.7% (84.5-98.2%)	100%
PPV	20% (5-71.6%)	100%
NPV	64.1 (53.4-73.8%)	88.6% (78.7-94.9%)
LR+	0.02	53*
LR-	0.56	0.13
% Correct	61.9%	91.7%
Diagnostic Odds Ratio	0.03	410.8*

*Acronyms: CI – Confidence intervals; FOCUS – A FOCused method Utilizing hand-held echocardiography in Screening for RHD; LR+ – Positive likelihood ratio test; LR- – Negative likelihood ratio test; NPV – Negative predictive value; PPV – Positive predictive value.*

*\* Contingency tables adjusted for 0 values according to Glas et al. (Glas et al., 2003)*

In reviewing the two categories of echocardiographic rheumatic heart disease separately, the sensitivity for detecting definite and borderline disease was 9.1% (95% CI 0.2 to 41.3%) and 0% respectively. The specificity for detecting both abnormal murmurs in definite and borderline disease was 95.2% (95% CI 86.5 to 98.9%). The positive predictive value was 20% (95% CI 5 to 71.6%) for definite disease. The negative predictive values were 86.8% (95% CI 76.4 to 93.7%) for definite and 72% (95% CI 60.9 to 81.3%) for borderline disease respectively. The test reliability was 82.2% for definite disease and 68.6% for borderline disease, with a diagnostic odds ratio of 1.48 and 0.28 (adjusted) for detecting definite and borderline disease respectively, as depicted in Tables 5.2 and 5.3.

#### *FOCUS protocol: Test characteristics*

The average time to record the images using the focused protocol with hand-held echocardiography was just under two minutes (mean 117 seconds  $\pm$  22 seconds). No technical difficulties were encountered. The sensitivity of the FOCUS protocol together with hand-held echocardiography in order to identify correctly cases of definite or borderline rheumatic heart disease was 76.5% (95% CI 58.8 to 89.3%). The specificity was 100%. Accordingly, the positive predictive value was also 100%, while the negative predictive value was 88.6% (95% CI 78.7 to 94.9%). The adjusted likelihood ratios were 53 (positive likelihood ratio) and 0.13 (negative likelihood ratio) respectively, with a percentage of correct diagnosis of 91.7% and an adjusted diagnostic odds of 410.8.

Reviewing the two categories of borderline and definite rheumatic heart disease individually shows that the test statistics improved for definite disease and worsened for borderline disease. The sensitivity for definite and borderline disease was 92.3% (95% CI 63.9 to 99.8) and 66.7% (95% CI 43 to 85.4%) respectively. The specificity for detecting definite and borderline disease was 100% in both groups. The test reliability was 98.7% for detecting definite disease and 91.4% for detecting borderline disease, with the adjusted diagnostic odds ratio being 1562.5 and 241.7 for detecting definite and borderline disease respectively, as depicted in Tables 5.2 and 5.3.



Table 5.2. Performance characteristics of alternate modalities to identify definite rheumatic heart disease

Performance characteristics	Computer-assisted auscultation %( 95% CI)	Hand-held echocardiography and FOCUS protocol %(95% CI)
<b>Sensitivity</b>	9.1% (0.2-41.3%)	92.3% (63.9-99.8%)
<b>Specificity</b>	95.2% (86.5-98.9%)	100%
<b>PPV</b>	20% (5-71.6%)	100%
<b>NPV</b>	86.8% (74.6-93.7%)	98.4% (91.5-99.99%)
<b>LR+</b>	0.25	25*
<b>LR-</b>	0.17	0.016
<b>% Correct</b>	82.2%	99%
<b>Diagnostic Odds Ratio</b>	1.48	1562.5*

Acronyms: CI – Confidence intervals; FOCUS – A FOCused method Utilizing hand-held echocardiography in Screening for RHD; LR+ – Positive likelihood ratio test; LR- – Negative likelihood ratio test; NPV – Negative predictive value; PPV – Positive predictive value.

\* Contingency tables adjusted for 0 values according to Glas et al. (Glas et al., 2003)

Table 5.3. Performance characteristics of alternate modalities in identifying borderline rheumatic heart disease

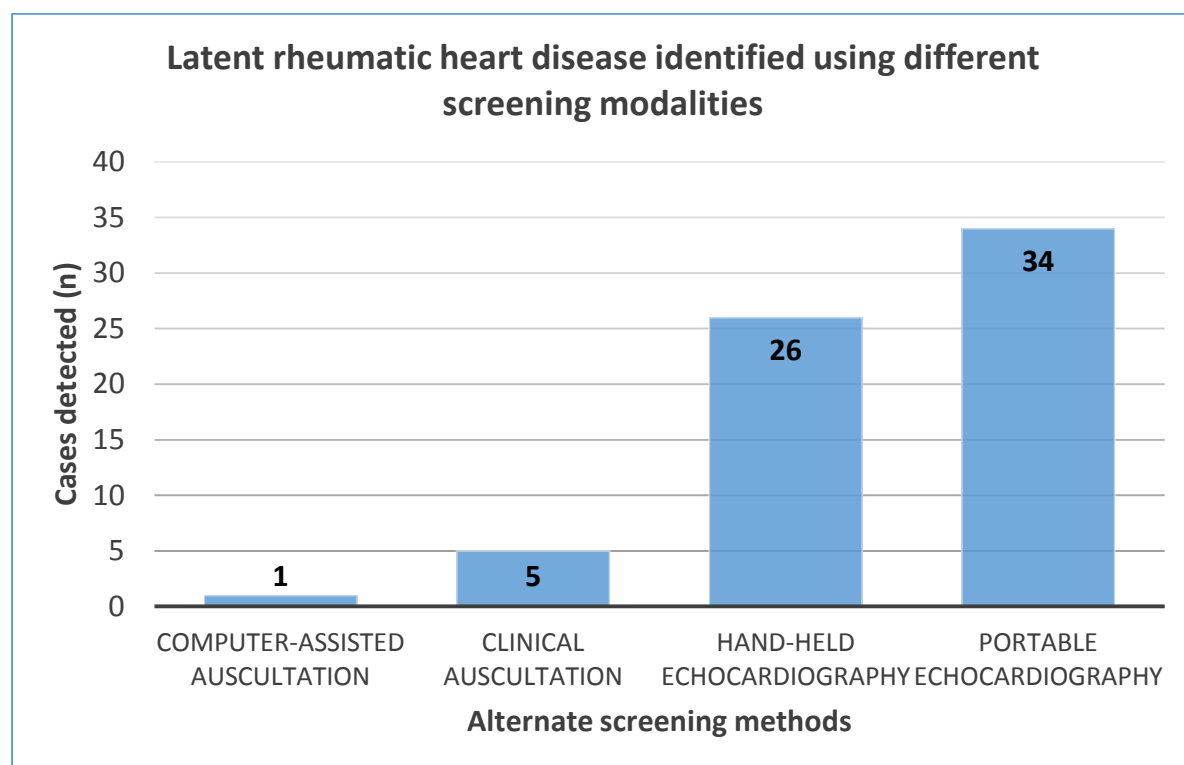
Performance characteristics	Computer-assisted auscultation %( 95% CI)	Hand-held echocardiography and FOCUS protocol %(95% CI)
<b>Sensitivity</b>	0%	66.7% (43-85.4%)
<b>Specificity</b>	95.2% (86.5-98.9%)	100%
<b>PPV</b>	10%*	100%
<b>NPV</b>	72% (60.9-81.3%)	89.9% (80.2-95.8%)
<b>LR+</b>	0.11*	29*
<b>LR-</b>	0.39	0.13
<b>% Correct</b>	68.6%	92%
<b>Diagnostic Odds Ratio</b>	0.28*	241.7*

Acronyms: CI – Confidence intervals; FOCUS – A FOCused method Utilizing hand-held echocardiography in Screening for RHD; LR+ – Positive likelihood ratio test; LR- – Negative likelihood ratio test; NPV – Negative predictive value; PPV – Positive predictive value.

\* Contingency tables adjusted for 0 values according to Glas et al. (Glas et al., 2003)

## 5.5 Discussion

Our study has three key findings. Firstly, computer-assisted auscultation performs dismally in detecting asymptomatic rheumatic heart disease. The modality was worse than standard auscultation in detecting cases of asymptomatic rheumatic heart disease (Figure 5.1). Secondly, focused hand-held echocardiography, which can be carried out within 2 minutes per study, has a moderate sensitivity, and high specificity and diagnostic odds for detection of asymptomatic rheumatic heart disease. Thirdly, the sensitivity of hand-held echocardiography is higher for definite rheumatic heart disease compared to borderline status.



Acronyms: n=number

Figure 5.1 Cases identified using different screening methods

The focused protocol defines a simplified method of using a single criterion with hand-held echocardiography to screen for asymptomatic rheumatic heart disease. This confirms the need as demonstrated by Reeves, (Reeves et al., 2011) Mirabel (Mirabel et al., 2012a) and Beaton (Beaton et al., 2012; Beaton et al., 2014a) (Beaton et al., 2015) to develop a simple method for the large-scale screening for rheumatic heart disease in low-resource settings. Reeves and Mirabel investigated the use of shorter echocardiography protocols used with standard portable

echocardiography machines, while Beaton employed the hand-held echocardiography machine with modified World Heart Federation criteria. Mirabel also recently reported the use of a short echocardiography protocol with hand-held echocardiography- utilising mitral and aortic regurgitant jet lengths. (Mirabel et al., 2015) Lu et al found that mitral regurgitation  $> 1.5$  cm and any aortic incompetence was superior to mitral regurgitation alone in optimizing sensitivity and specificity. (Lu et al., 2015) Our study used only the single-jet criterion with hand-held echocardiography for the screening of asymptomatic rheumatic heart disease. This criterion was chosen because pathological mitral regurgitation has been demonstrated in a previous study to be an independent predictor for the progression or persistence of mild valvular lesions (Zühlke 2014, submitted).

Screening by using a test with high sensitivity but low specificity will result in many participants needing expensive further investigation, which is an untenable situation in low-resource settings. This has been a criticism of screening criteria prior to the publication of the WHF criteria (DeGroff, 2010; Kothari, 2010). We have found, however, that this protocol has sufficiently high sensitivity and reliability to be feasible for use as a screening test for definite rheumatic heart disease in high-prevalence communities. It has already been established that the WHF criteria are appropriately specific for their confirmatory function (Roberts et al., 2013b).

Table 5.4. Classification of definite and borderline cases

<b>Definite RHD</b>	<b>Cases</b>	<b>CAA</b>	<b>Hand-held Echocardiography with FOCUS protocol</b>
Morphological features of MV plus MR	12	1	12
Mitral Stenosis	0	0	0
Morphological features of AV plus AR	1	0	0
Borderline disease of MV and AV	0	0	0
<b>Total</b>	<b>13</b>	<b>1</b>	<b>12</b>

<b>Borderline RHD</b>	<b>Cases</b>	<b>Hand-held Echocardiography with FOCUS protocol</b>
At least two morphological features of MV	6	1
Pathological MR	15	13
Pathological AR	0	0
At least two morphological features of AV	0	0
<b>Total</b>	<b>21</b>	<b>14</b>

*Acronyms: AR – aortic regurgitation; AV – aortic valve; CAA – Computer-assisted auscultation; FOCUS – A FOCused method Utilizing hand-held echocardiography in Screening for RHD; MR – mitral regurgitation; MV – mitral valve; RHD – Rheumatic Heart Disease.*

We acknowledge that the focused echocardiography protocol criteria failed to detect a proportion of cases of borderline disease, specifically ones that were only affecting the morphology of the mitral or aortic valves (Table 5.4). To date, screening studies have been characterised by findings of mitral regurgitation in over 95% of definite disease (Paar et al., 2010; Reeves et al., 2011). These have also been found to be the most useful in pilot studies and other short protocols (Beaton et al., 2014a; Colquhoun et al., 2013; Reeves et al., 2011). Although the role of morphological abnormalities is clear in the determination of definite disease, borderline disease has been shown to have a variable outcome, from worsening to normalising in a significant proportion. The implications of missing a large number of borderline cases are unknown.

Several reports demonstrate that cardiac auscultation is insufficiently sensitive when screening for rheumatic heart disease (Bhaya et al., 2010; Godown et al., 2015; Kane et al., 2012; Marijon et al., 2007; Saxena et al., 2013; Steer et al., 2009b). The use of an automated decision in combination with digital auscultation may improve the sensitivity and specificity of murmur detection, (Tavel, 2006, 2010) and the method furthermore has merit in terms of the teaching and training of health professionals (Zühlke et al., 2012a). We have demonstrated unequivocally, however, that computer-assisted auscultation has no place in the screening for asymptomatic rheumatic heart, faring worse than ordinary cardiac auscultation. Although auscultation remains cheap, easy to use in all settings and shows increased specificity when used with an algorithm, its role as a screening tool for large-scale rheumatic heart disease screening is limited.

The World Health Organization has identified the establishment of national programmes for the prevention and control of acute rheumatic fever/rheumatic heart disease, as a national priority for high-prevalence communities (WHO, 2004). Thus far, however, the vast majority of screening programmes have been isolated research projects, not embedded within existing control programmes. This protocol has the potential to position future screening programmes within rheumatic heart disease prevention and control programmes. In addition, the point-of-care application of hand-held echocardiography to diagnose systolic dysfunction, advance antenatal care and include vascular scanning aligns this protocol with integrated models of care, where rheumatic heart disease could form one of the diseases easily screened for and managed by primary care teams (Mayosi, 2012). However, further studies are needed to show that screening changes outcomes, before it is likely to be adopted for wide use.

The costs reported by Reeves et al., using a non-cardiologist reviewer, a lower-cost echocardiography machine and a shortened scanning time, were remarkably low at a cost-per-patient screened of US\$2.07 and a cost-per-case of definite rheumatic heart disease detected of US\$37.75 (Reeves et al., 2011). We envision that this protocol will be similarly cost-efficient, and thus affordable, in low-income countries. An additional cost of screening relates to the expert personnel needed to perform and review echocardiograms. With this method, it will be relatively easy to teach non-expert operators to perform scans, thus reducing costs considerably. Further research that looks at a cost-effectiveness analysis of a programme based on this protocol and the training and implementation of a non-cardiologist is the natural extension of this study. A study is underway to train radiology and nursing staff to implement this protocol and screen larger numbers of children in Zambia (Mayosi et al., 2014).

This study has several limitations. We used a small sample of cases of asymptomatic rheumatic heart disease. However, the confidence intervals around the estimates were small, suggesting that the sample size was adequate for the purposes of this study. Secondly, the study was conducted by a cardiologist who performed the auscultation and the echocardiography. **Thirdly, we did not evaluate the utility of shorter mitral regurgitant jets less than 2cm as performed by Lu et al.**<sup>(Lu et al., 2015)</sup> We elected to use the standard definition of 2 cm or greater as pathological.(Minich et al., 1997) The findings may therefore not be generalizable to the performance of this study by minimally trained health staff. Finally, the use of a single observer means that the reproducibility of the measurements in this study is unknown.

## 5.6 Conclusion

FOCUS, a FOCused method Utilizing hand-held echocardiography in Screening for rheumatic heart disease, is a simple, short, sensitive and highly specific method of screening for rheumatic heart disease that is suited to low-income settings, because it incorporates hand-held ultra-portable echocardiography and a single criterion. However, computer-assisted auscultation is not a suitable screening modality for asymptomatic rheumatic heart disease due to extremely low sensitivity.

## **6 Study 4: Baseline characteristics, complications, and gaps in evidence-based interventions in 3,343 children and adults with rheumatic heart disease**

### **6.1 Abstract**

#### *Introduction*

Rheumatic heart disease (RHD) accounts for over a million premature deaths annually; however, there is little contemporary information on presentation, complications, and treatment.

#### *Methods*

This prospective registry enrolled 3343 patients (median age 28 years, 66.2% female) presenting with RHD at 25 hospitals in 12 African countries, India and Yemen between January 2010 and November 2012.

#### *Results*

The majority (63.9%) had moderate to severe multivalvular disease, complicated by congestive heart failure (33.4%), pulmonary hypertension (28.8%), atrial fibrillation (AF) (21.8%), stroke (7.1%), infective endocarditis (IE) (4%), and major bleeding (2.7%). One quarter of adults and 5.3% of children had decreased left ventricular (LV) systolic function; 23% of adults and 14.1% of children had dilated LVs. Fifty-five percent (n=1,761) of patients were on secondary antibiotic prophylaxis. Oral anticoagulants were prescribed in 69.5% (n=946) of patients with mechanical valves (n=501), AF (n=397), and high-risk mitral stenosis in sinus rhythm (n=48). However, only 28.3% (n=269) had a therapeutic international normalised ratio (INR). Among 1825 women of child-bearing age (12-51 years), only 3.7% (n=65) were on contraception. The utilisation of valvuloplasty and valve surgery was higher in upper-middle compared to lower-income countries.

#### *Conclusion*

RHD patients were young, predominantly female, and had a high prevalence of major cardiovascular complications. There is suboptimal utilisation of secondary antibiotic prophylaxis, oral anticoagulation, and contraception, and variations in the use of percutaneous and surgical interventions by country income level.

## 6.2 Introduction

Rheumatic heart disease (RHD) is one of the leading non-communicable diseases in low- and middle-income countries, and accounts for up to 1.4 million deaths per year (Carapetis et al., 2005; Paar et al., 2010). These deaths are due to the sequelae of RHD, including atrial fibrillation (AF), infective endocarditis (IE), and pregnancy-associated complications (Benjamin et al., 1998; Diao et al., 2011; Koegelenberg et al., 2003). Despite the magnitude of the problem, there is little systematically collected contemporary data on the characteristics of the disease and on the treatments, complications and long-term outcomes of patients with RHD (Carapetis, 2008). The proposal of the World Heart Federation to reduce mortality from RHD by 25% by the year 2025 requires an understanding of the contemporary characteristics and use of proven interventions among patients living in endemic countries (Remenyi et al., 2013).

Much of the morbidity and mortality due to RHD could be prevented by existing therapies (Lawrence et al., 2013; McDonald et al., 2006). There is good evidence to suggest that secondary prophylaxis with long-acting penicillin reduces the recurrence of episodes of ARF (Manyemba and Mayosi, 2003). International guidelines advocate the use of oral anticoagulants (OACs) among patients with rheumatic AF. Where severe symptoms have developed, with or without congestive cardiac failure (CCF), percutaneous or surgical interventions are indicated (Nishimura et al., 2014). However, reports from developing countries have documented inadequate adherence to secondary prophylaxis and poor control of OAC (Bassili et al., 2000; Oldgren et al., 2014; Pelajo et al., 2010). In addition, limited numbers of centres provide percutaneous and surgical interventions in developing countries (Zühlke et al., 2013).

The Global RHD Registry (REMEDY) was designed to assemble a contemporary cohort of RHD patients from developing countries in order to evaluate comprehensively both disease and treatment patterns, with particular reference to valvular involvement; the prevalence of adverse cardiac events and pharmacological treatments used; and the use of percutaneous and surgical interventions.

## 6.3 Methods

The design and method used in this particular study has been described in detail in Section 2.5 of this thesis. To recap briefly, REMEDY is a multicentre, international hospital-based prospective

registry of patients with RHD (Karthikeyan et al., 2012a). This report describes the characteristics of patients enrolled; the pharmacological treatments used; particularly secondary antibiotic prophylaxis, oral anticoagulation therapy, and contraception; and the use of percutaneous and surgical interventional procedures for valvular heart disease.

## 6.4 Results

### *Clinical characteristics and use of surgery*

In total, 3,343 participants with RHD were enrolled at participating sites between January 2010 and November 2012 (Appendix 1). Patients with RHD were young (median age 28 years), mainly female (66.2%), and largely unemployed (75.3%) (Table 6.1; Figure 6.1). There was a greater proportion of women in the childbearing age in low-income countries (86.5%) and lower-middle income countries (90.3%), compared with upper-middle income countries (66.9%) ( $P<0.01$ ).

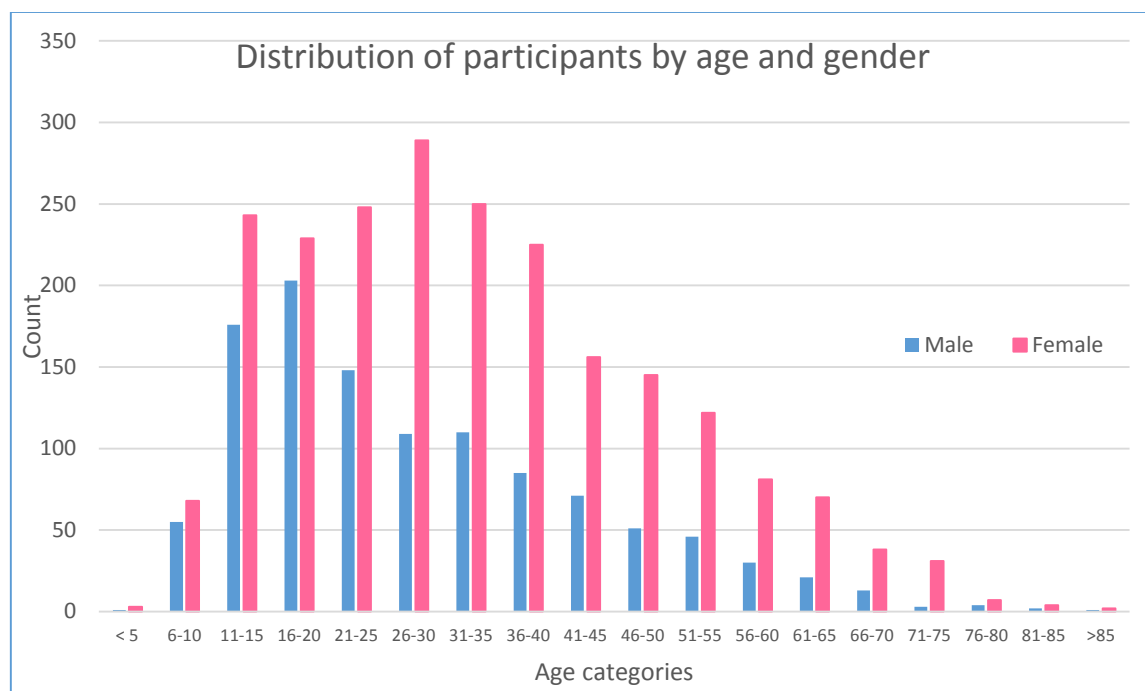


Figure 6.1. Age and gender distribution of 3,343 children and adults with rheumatic heart disease



Table 6.1. Demographic characteristics of 3,343 children and adults with rheumatic heart disease

	Low-income countries	Lower-middle-income countries	Upper-middle-income countries	P	Total
<b>Participants n (%)</b>	1,110 (33.2)	1,370 (41.0)	863 (25.8)		3,343
<b>Age, median [IQR]<sup>a</sup></b>	24 [15-34]	28 [18-38]	39 [22-52]	0.4	28 [18-40]
<b>Women n (%) <sup>a</sup></b>	728 (65.8)	867 (63)	616 (71.3)	0.33	2,211 (66.2)
<b>Women in childbearing age n (%) <sup>#a</sup></b>	630 (86.5)	783 (90.3)	412 (66.9)	<0.01	1,825 (82.5)
<b>Children n (%) <sup>*</sup></b>	405 (36.6)	349 (25.5)	167 (19.4)	0.54	921 (27.6)
<b>Adults with no formal schooling n (%) <sup>a</sup></b>	66 (9.5)	354 (34.9)	38 (5.5)	<0.01	458 (19.1)
<b>Completed primary-level schooling</b>	246 (35.2)	278 (27.4)	204 (29.6)		728 (30.3)
<b>Completed secondary-level schooling</b>	373 (53.4)	372 (36.7)	436 (63.3)		1,181 (49.2)
<b>Completed tertiary-level education</b>	13 (1.98)	10 (1.0)	11 (1.6)		34 (1.4)
<b>Unemployed adults n (%) <sup>*,a</sup></b>	529 (75.4)	766 (75.1)	520 (75.5)	0.98	1,815 (75.3)

*\*Children are defined as younger than 19 years of age; \*Adults are 19 years or older; #Defined as between the ages of 12-51 years; <sup>a</sup> available data*

Table 6.2. Clinical characteristics of 3,343 children and adults with rheumatic heart disease

		Low-income countries (N 1110) N (%)	Lower-middle income countries (N 1370) N (%)	Upper-middle income countries (N 863) N (%)	Total N (%)	P
<b>NYHA III &amp; IV</b>		306 (27.6)	384(29.1)	119 (13.9)	809 (24.6)	0.24
<b>Medical history</b>	<b>Acute Rheumatic Fever</b>	247 (22.3)	593 (44.3)	500 (59.0)	1340 (40.7)	0.06
	<b>Congestive Heart Failure</b>	476 (43.0)	285 (21.0)	349 (40.6)	1110 (33.4)	0.06
	<b>Pulmonary Hypertension</b>	329 (29.9)	465 (34.2)	163 (19)	957(28.8)	0.5
	<b>Stroke</b>	58 (5.2)	52 (3.8)	125 (14.5)	235 (7.1)	<0.01
	<b>Infective Endocarditis</b>	25 (2.3)	59 (4.36)	49 (5.7)	133 (4.0)	0.1
	<b>Major Bleeding</b>	21 (1.9)	38 (2.8)	30 (3.5)	89 (2.7)	0.61
	<b>Peripheral Embolism</b>	3 (0.3)	3 (0.2)	19 (2.2)	25 (0.8)	<0.001
	<b>Cardiovascular Complications <sup>a</sup></b>	96 (8.7)	137 (10.1)	191 (22.2)	424 (12.7)	0.02
<b>Atrial Fibrillation</b>		163 (17.9)	241 (22.0)	182 (22.7)	586(21.8)	0.49
<b>Echocardiography</b>	<b>Decreased LVEF in adults</b>	223 (20.6)	262 (19.8)	176 (22.2)	661 (26.5)	0.58
	<b>Decreased LVEF in children</b>	67 (6.2)	83 (6.3)	18 (2.3)	168 (5.3)	<0.01
	<b>Dilated LVEDD in adults</b>	260 (23.9)	302 (22.7)	180 (22.3)	742 (23.0)	0.81
	<b>Dilated LVEDD in children</b>	191 (17.6)	177 (13.3)	86 (10.7)	454 (14.1)	0.3
	<b>Left atrial thrombus</b>	19 (1.8)	18 (1.4)	7 (0.8)	44 (1.4)	0.6
<b>Surgery</b>	<b>Valve replacement or repair</b>	81 (11.3)	199 (27.8)	435 (60.8)	715(21.45)	<0.01
	<b>Mechanical valve only</b>	55 (93.2)	139 (88.5)	353 (94.9)	547(93.0)	0.1

<sup>a</sup>Composite of stroke, Infective endocarditis, major bleeding and peripheral embolism. <sup>\*\*</sup>Denotes the total number of participants with data

Acronyms: AO – aorta; LA – left atrium; LVEDD – left ventricular end diastolic diameter; LVEF – left ventricular ejection fraction; NYHA – New York Heart Association functional class; TIA – transient ischaemic attack.

AF was documented in 586/2688 (21.8%) of patients by means of electrocardiograms performed at the time when they enrolled in the study (Table 6.2). There was a substantial variation in the clinical features and use of percutaneous and surgical interventions between the different income groups in the various countries (Table 6.2). Stroke, peripheral embolism and cardiovascular complications, in general, were reported more frequently among patients living in UMICs (14.5%, 2.2%, and 22.2% respectively) compared with those from LMICs (3.8%, 0.2%, and 10.1% respectively) and LICs (5.2%, 0.3%, and 8.7% respectively) ( $P=0.02$ ). Of the 586 (21.8%) patients with AF, 17.9%, 21.9%, and 26.7% lived in LICs, LMICs and UMICs respectively. The proportion of children with a decreased left ventricular ejection fraction was lower in UMICs than in LMICs and LICs ( $P<0.01$ ). The use of valve replacement/repair and valvuloplasty increased with rising country income levels ( $P<0.03$ ) (Table 6.2; Figure 6.2).

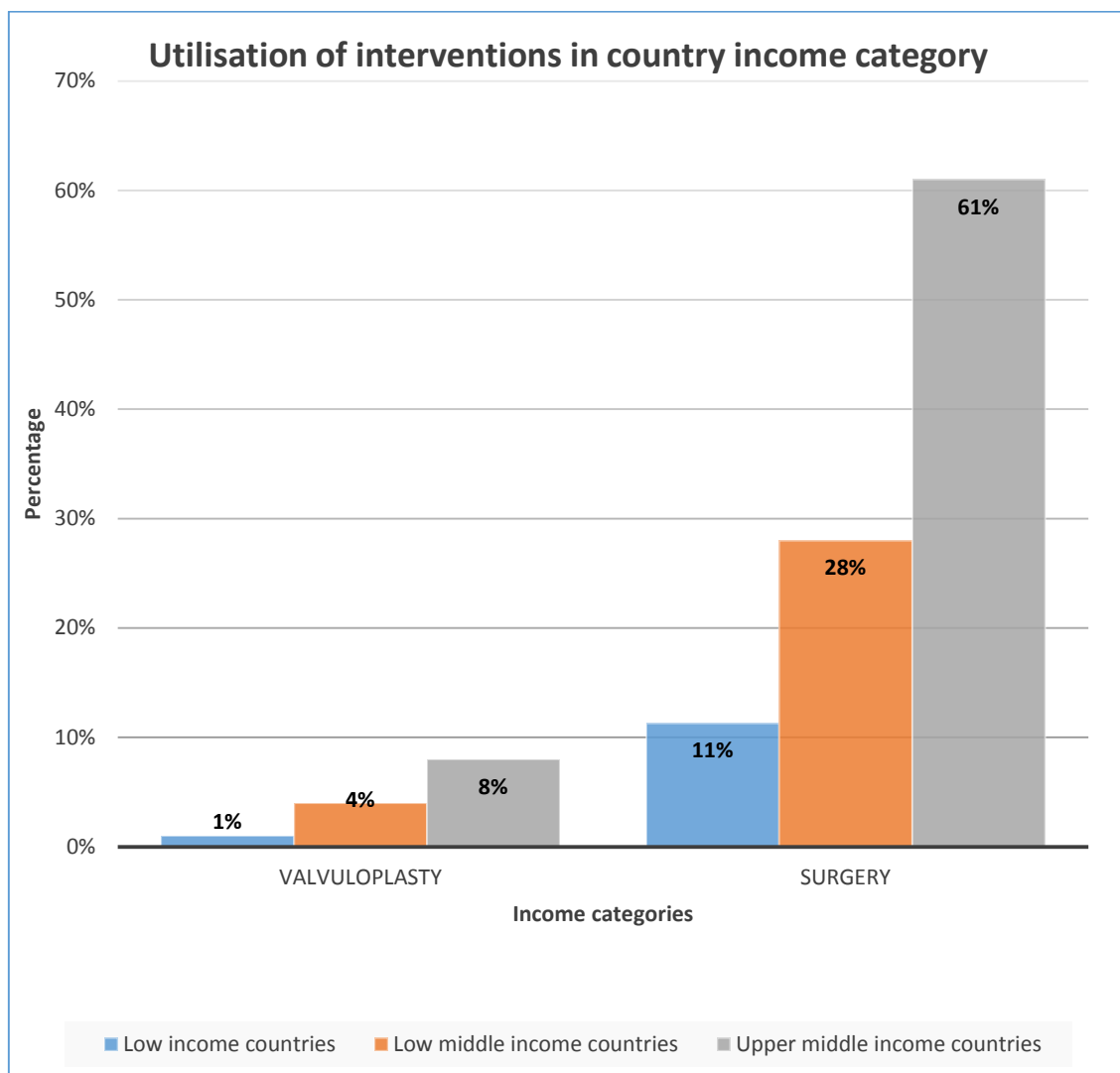
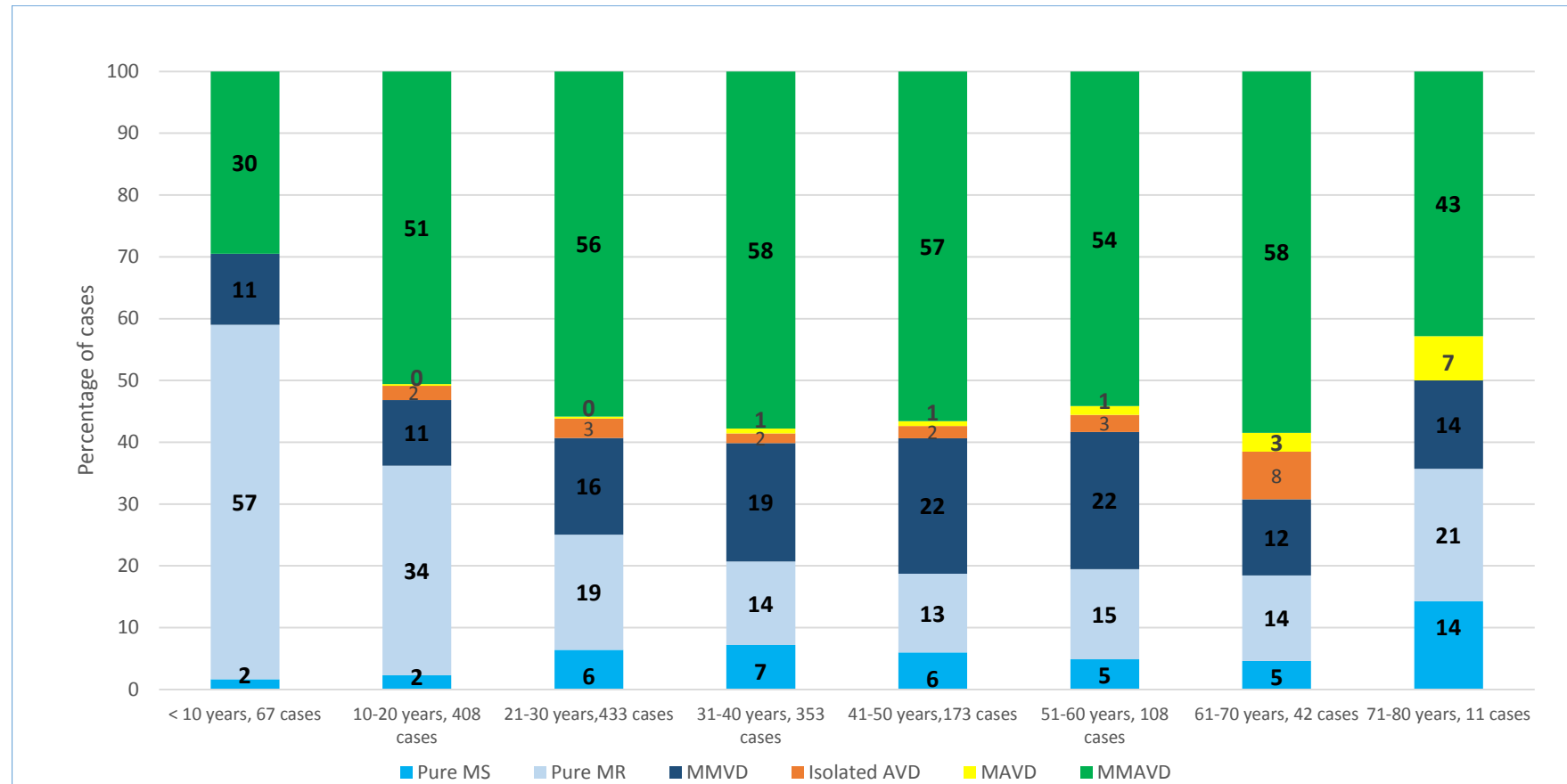


Figure 6.2. Utilisation of valve surgery and valvuloplasty from different income category countries

*Pattern and severity of native valve disease*

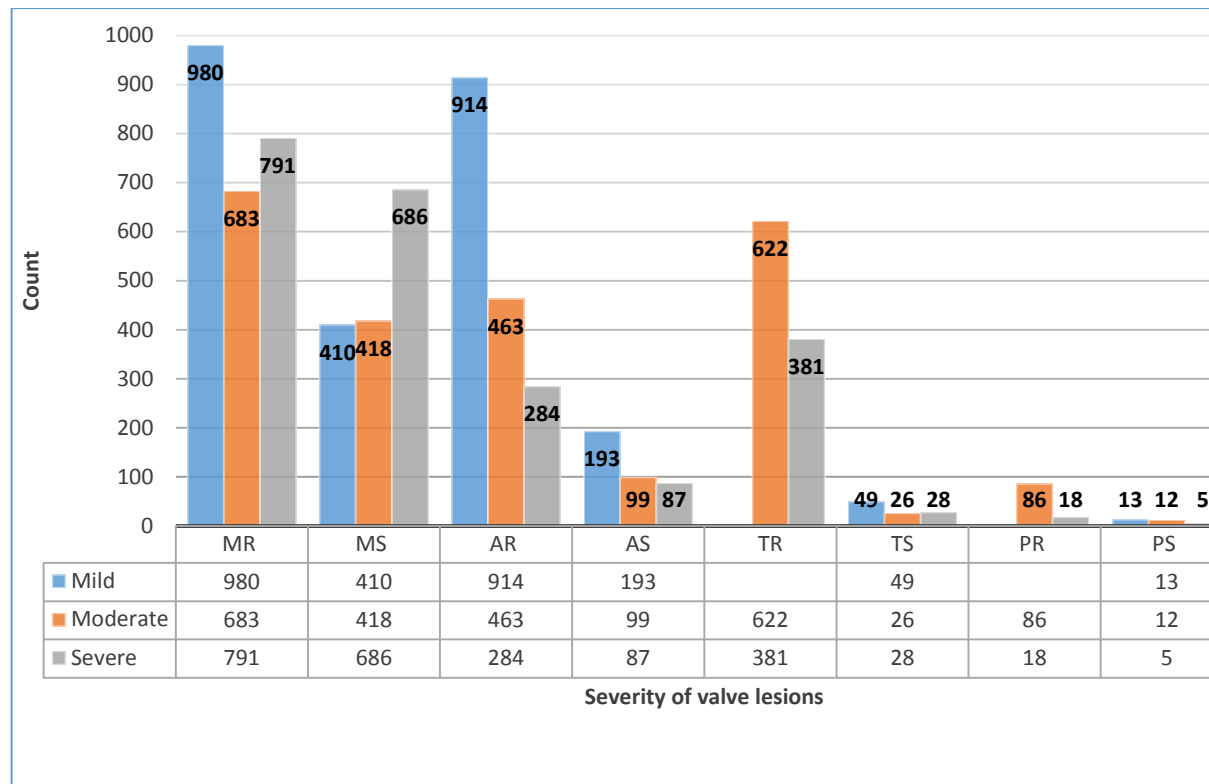
Figure 6.3 demonstrates the pattern of valve disease by age group in patients without percutaneous or surgical intervention. Children in the first decade of life presented predominantly with pure mitral regurgitation, with mixed mitral and mixed aortic valve disease emerging as a dominant mitral valve lesion from the second decade of life onwards. The frequency of pure mitral stenosis, isolated aortic valve disease (i.e., aortic stenosis or aortic regurgitation [AR]) and mixed aortic valve disease without mitral disease was low in early life, and increased with age.

Mitral regurgitation was the commonest organic valve lesion (82.0%), followed by AR (52.7%), mitral stenosis (48.9%), aortic stenosis (10.6%), tricuspid stenosis (2.6%), and pulmonary stenosis (1%) (Figure 6.4). The majority of cases of mitral stenosis (76.9%), mitral regurgitation (62.4%), pulmonary stenosis (61.5%), tricuspid stenosis (54.4%), and aortic stenosis (53.6%) were moderate to severe, whereas the majority of cases of AR (52%) were mild. Patients who had not had surgery had a dilated left ventricle (LV) in 23% (n=581) of the adults and 16.4% (n=413) of the children, and a decreased ejection fraction (EF) in 18.3% (n=460) of adults and 5.6% (n=140) of children. There was a gradient as patients increased in age for dilated LV ( $P<0.0001$ ) and falling LVEF ( $P<0.0001$ ), which suggest disease progression.



Acronyms: AVD – aortic valve disease; MAVD – mixed aortic valve disease; MMAVD – mixed mitral and aortic valve disease; MMVD – mixed mitral valve disease; MR – mitral regurgitation; MS – mitral stenosis.

Figure 6.3. The pattern of native rheumatic valve disease in 2,475 children and adults



*Acronyms: AR – aortic regurgitation; MR – mitral regurgitation; MS – mitral stenosis; PR – pulmonary regurgitation; PS – pulmonary stenosis; TR – tricuspid regurgitation; TS – tricuspid stenosis.. Only moderate and severe TR and PR are included in the study.*

Figure 6.4. Severity of all rheumatic valve lesions with echocardiograms at enrolment

### *Use of secondary prophylaxis*

Overall, 55% of participants were on secondary penicillin prophylaxis. Intramuscular penicillin was the most common mode of administration, used by 1,926 (89.4%) of the cohort; the remainder (227, 11.5%) were on either oral penicillin or erythromycin (data available with regard to 2,153). The administration of secondary prophylaxis differed by country income group: 69.8% in LICs, 59.7% in LMICs and 29.2% in UMICs ( $P<0.001$ ) (Figure 6.5). Whereas oral and parenteral antibiotics were used in almost equal proportions in UMICs, nearly all participants on secondary prophylaxis received intramuscular penicillin in LMICs and LICs. The adherence to secondary antibiotic prophylaxis was higher in children compared with adults, for both benzathine penicillin ( $81.8\pm30.8\%$  versus  $76.9\pm33.1\%$ ,  $P<0.01$ ) and oral antibiotics ( $83.1\pm24.9\%$  versus  $75.0\pm36.6\%$ ;  $P<0.01$ ) respectively. Post-surgery patients were less likely to be on secondary prophylaxis compared with those awaiting surgery (31.1% compared with 61.5%,  $P<0.05$ ). Patients on a 2-weekly intramuscular regime showed lower levels of adherence (68.4%) than those on either a 3-weekly (76.0%) or 4-weekly regimen (82.8%) ( $P<0.05$ ).

### *Use of oral anticoagulants and other medications*

There were 1,362 (40.7%) patients with mechanical heart valves, AF and severe mitral stenosis in sinus rhythm with dilated left atria or the presence of left atrial thrombus, which are indications for oral anticoagulants (OAC) in RHD (Table 6.3) (Nishimura et al., 2014). OACs were prescribed in 69.5% (946) of patients with these indications. Of the patients on OACs for the recognised indications, 12.2% (115) had had no INR monitoring, whereas 34.1% (323) had only one to three INR tests in the six months preceding enrolment. The INR at enrolment was sub-therapeutic in 32.7% (309), therapeutic in 28.3% (268), and above the therapeutic range in 17.7% (167) (no INR testing on the remainder of 21.4% (202) (Figure 6.6). Sixty percent of participants were unaware of the therapeutic range of INR values.

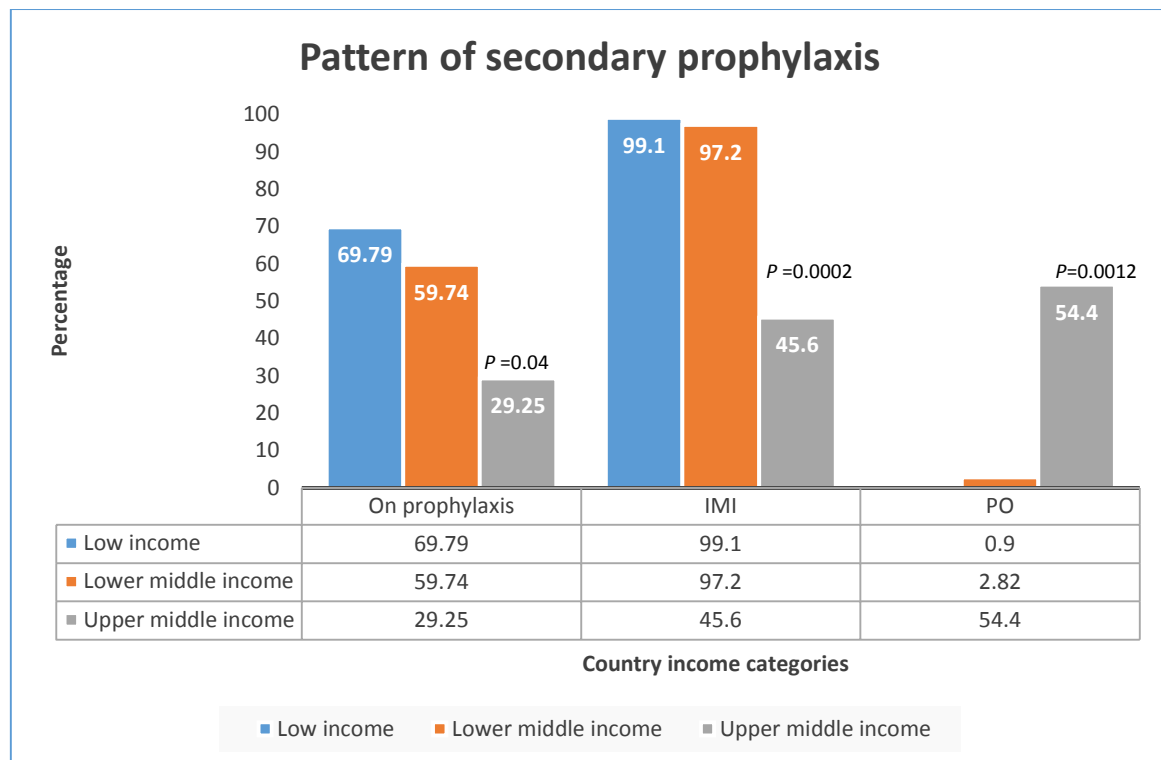


Figure 6.5. Adherence to penicillin secondary prophylaxis

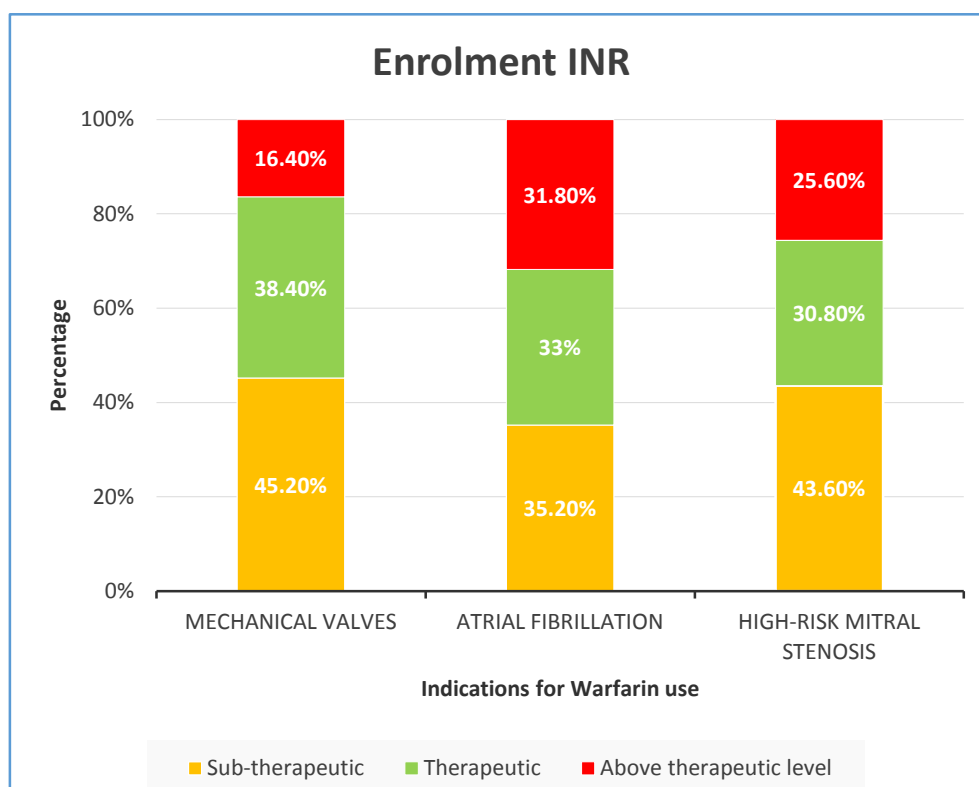


Figure 6.6. INR-categories at enrolment



Table 6.3. Use of anti-thrombotic medication and quality of anticoagulation in patients with an indication for oral anticoagulant therapy

Indication	Antithrombotic medication	N (%)	Details	N (%)*
Mechanical valves	Warfarin	501 (91.6)	No INR tests done in 6 months prior to enrolment	28 (5.6)
			1-3 INR tests done 6 months prior to enrolment	155 (30.9)
			Enrolment INR tests <2.5	198 (39.5)
			Enrolment INR tests in 2.5-3.5 range	168 (33.5)
			Enrolment INR tests >3.5	72 (14.4)
	None	41 (7.5)		
	Aspirin	5 (0.9)		
	Total	547		
Atrial fibrillation	Warfarin	397 (67.8)	No INR tests done in 6 months prior to enrolment	58 (14.6)
			1-3 INR tests done 6 months prior to enrolment	147 (37.0)
			Enrolment INR tests <2.0	94 (23.7)
			Enrolment INR tests in 2.0-3.0 range	88 (22.2)
			Enrolment INR >3.0	85 (21.4)
	None	126 (21.5)		
	Aspirin	55 (9.5)		
	Other (heparin)	8 (1.5)		
	Total	586		
Mitral stenosis in sinus rhythm and left atrial diameter ≥55 or left atrial thrombus	Warfarin	48 (20.3)	No INR tests done in 6 months prior to enrolment	29 (60.4)
			1-3 INR tests done 6 months prior to enrolment	21 (43.8)
			Enrolment INR tests <2.0	17 (35.4)
			Enrolment INR tests in 2.0-3.0 range	12 (25.0)
			Enrolment INR >3.0	10 (20.8)
	None	169 (71.6)		
	Aspirin	19 (8.0)		
	Total	236		

There was a high use of additional medication: 68% of patients were on diuretics, 40% on beta-blockers, 35% on digoxin, and 5% on other antiarrhythmic drugs. Among women of childbearing age (12-51 years; n=1825), only 3.6% (65) were on contraceptive medication. Seventy-three women (3.9%) were pregnant at the time of enrolment, the youngest being 14 years of age, and the oldest 51 years of age. In total, 15 (20.6%) pregnant women were on Warfarin.

## 6.5 Discussion

To the best of our knowledge, REMEDY is the first multicentre and multinational prospective study of the clinical features of RHD and the use of evidence-based interventions and outcomes in children and adults with RHD from lower-income countries (LIC) and middle-income countries (LMIC). The baseline characteristics reported here reveal five main findings. Firstly, the patients with RHD who live in low- and middle-income countries tend to be young and largely female, and to have a high unemployment rate. Secondly, the majority have moderate to severe valvular heart disease that is associated with pulmonary hypertension and left ventricular dysfunction in up to a quarter of patients. Thirdly, there is inadequate use of secondary antibiotic prophylaxis in developing countries, with a lack of preventive treatment in nearly half of the patients. Fourthly, while the use of OACs in patients with appropriate indications is relatively high, the quality of anticoagulation control at enrolment with the study was poor, with less than a third of INR tests being in the therapeutic range. Finally, there were variations between LICs, LMICs and upper-middle income countries (UMICs) in the ascertainment and prevalence of cardiovascular complications, and the use of percutaneous and surgical interventions for RHD.

It is well established that RHD is a chronic disease of the young that accounts for the greatest cardiovascular-related loss of disability-adjusted life years in children (Wang et al., 2012b). The high prevalence of unemployment among patients with RHD in LMICs is consistent with findings from reviews of the role of environmental factors (Steer et al., 2002). While the predominance among females is well recognised (Lawrence et al., 2013), the prominence of RHD among women of reproductive age has major implications for the reproductive health of women living in developing countries (Mocumbi and Sliwa, 2012). Pregnancy with RHD is high risk, and is one of the major non-obstetric causes of maternal death in Africa (Diao et al., 2011; Watkins et al., 2012). The extremely low rate of use of contraception in this cohort is alarming, and may reflect the poor provision of family planning and pre-pregnancy advice for women with heart disease in many regions of the world (Mocumbi and Sliwa, 2012; Thorne et al., 2006). We found that 20.6% of

women who were pregnant were on Warfarin, despite the known teratogenicity of the agent. This calls for safer alternatives in these women.

In this study, the pattern of rheumatic valve involvement that is characterised by pure mitral regurgitation in the first two decades of life is similar to what has been observed previously (Demirbag et al., 2013; Sani et al., 2007a; Sliwa et al., 2010; Tantchou Tchoumi and Butera, 2013). This study, however, enrolled patients with moderate to severe rheumatic valve disease that was associated with pulmonary hypertension and left ventricular dysfunction in a substantial proportion of cases. The enrolment of severe cases reflects the patterns of referral to the participating sites, which generally served as tertiary centres in their countries. These patients are at high risk of developing IE, and will require surgical intervention. In the Heart of Soweto study, of 344 new cases of RHD who were seen at a tertiary centre, 22% required valve replacement/repair within a year, and 26% developed IE within 30 months (Sliwa et al., 2010).

Effective RHD control programmes focus on secondary prevention in the form of regular long-acting intramuscular penicillin injections (Nordet et al., 2008). While the effectiveness of secondary prevention is proven, implementation is difficult and extremely variable, both in and between countries (Remond et al., 2013). Low uptake has been highlighted in numerous countries (Bassili et al., 2000; Lue et al., 1976; Pelajo et al., 2010; Walker et al., 1987). The WHO recommends the life-long use of antibiotic prophylaxis to prevent ARF in patients with severe RHD, such as those enrolled in this study (WHO Technical Report Series, 2004). However, nearly half of the participants in this study were not on antibiotic prophylaxis at the time of enrolment. There is thus clearly a need to identify barriers and enhance the delivery of secondary prophylaxis for RHD within the framework of the care for chronic diseases in LMICs (Wagner et al., 2001).

OACs are recommended in patients with mechanical heart valves, or valvular heart disease associated with AF, or in patients in sinus rhythm with mitral stenosis associated with a high-risk factor, such as the presence of left atrial thrombus or a dilated left atrium >55mm (De Caterina et al., 2013). In the present study, OACs were prescribed in 78% of patients with these indications, which is higher than the 58% use of OAC found in a world-wide registry of non-rheumatic AF (Oldgren et al., 2014). INR control was poor, however, with about one in five patients requiring OACs having therapeutic INR levels at the time of enrolment. Alternative strategies for improving anti-coagulation in LMICs need to be considered, including the use of fixed-dose Warfarin, point-of-care INR testing, and trials of new forms of OACs in RHD patients with native valves

(Buchanan-Leel et al., 2002; Ellis et al., 2009; Okuyama et al., 2014; Ruff et al., 2014). This study provides a platform for trials of anticoagulation in RHD patients who have been excluded from virtually all randomised controlled trials of stroke prevention (Oldgren et al., 2014).

We observed variations in cardiovascular complications, AF, left ventricular dysfunction and the use of percutaneous and surgical intervention, categorised by country income status. The increasing prevalence of cardiovascular sequelae with rising income status was independent of age and similar to previous studies (Wang et al., 2013). The use of percutaneous and surgical interventions was extremely low in LICs compared with UMICs, despite the greater prevalence of patients with RHD and left ventricular dysfunction who require these interventions in LICs. These disparities in cardiovascular complications and the use of effective invasive interventions reflect differences in access to healthcare in LMICs.

There were several limitations to this study. As it was a hospital-based study, we therefore cannot address the burden of disease in the community. Participating centres were selected because of the availability of cardiology expertise and echocardiography facilities for the diagnosis of RHD. Therefore, this study enrolled cases of severe symptomatic RHD that are typically seen in tertiary centres. Furthermore, past events were self- or physician-reported, and were not adjudicated. Similarly, adherence to secondary prophylaxis was not verified by using pill counts or registers, as these were largely unavailable in the countries involved. However, INR measurements were verified from laboratory records. Finally, an additional limitation of the REMEDY baseline study is that we report observations of a cross-sectional study. The interpretation of the findings of a cross-sectional study is inherently limited. This applies particularly to comparisons across country income status, as those are prone to ecologic fallacy.

## **6.6 Conclusion**

There are gaps in the implementation of medical and surgical interventions of proven effectiveness for RHD in low- and middle-income countries. These include the need to improve access to penicillin for secondary prophylaxis, an improvement in the use and monitoring of oral anticoagulant therapy, the introduction of reproductive services for women with RHD, and efforts to improve access to percutaneous and surgical interventions by individual countries and the international community. Outcomes of clinical RHD need to be ascertained prospectively in order to respond to these urgent needs.

## **7 Study 5: Contemporary estimates of morbidity and mortality of rheumatic heart disease in South Africa: Outcomes from the Cape Town component of the global rheumatic heart disease registry**

### **7.1 Abstract**

#### *Introduction*

The Global Rhematic Heart Disease Registry (The REMEDY Study) is a prospective study of the baseline characteristics, complications and incidence of sequelae in RHD, and included 531 adults and children from Cape Town.

#### *Methods*

This report describes the characteristics and morbidity estimates at enrolment of patients from two South African sites. We also determine the incidence of adverse cardiovascular events: congestive cardiac failure (CCF), stroke, infective endocarditis, major bleeding, peripheral embolism, rheumatic fever recurrence, hospitalisation, surgery or intervention, pregnancy and all-cause mortality over a 24-month period.

#### *Results*

The RHD patients enrolled at the two Cape Town tertiary institutions are young, predominantly female, and largely post-surgical but with a high prevalence of complications at enrolment. Over the follow-up period, we documented an event rate of 203.56 per 1,000 person-years and an annual mortality rate of 4.1% in the Cape Town cohort. The most frequent event in the 24 month period was hospitalisation (13.2%/yr.) followed by surgery (4.24%/yr.), CCF (3.86%/yr), major bleeding and stroke (1.41/yr.). Enrolment in cardiac failure (hazard ratio 15.73, 95% CI 3.94 to 62.7,  $P<0.0001$ ) and development of a subsequent episode of congestive cardiac failure (CCF) conferred the highest risk of mortality (hazard ratio 11.1, 95% CI 5.6 to 21.96,  $P=0.047$ ).

#### *Conclusion*

RHD patients in Cape Town had a mortality rate of 4.1%, which was comparable with the general population. There is a heavy burden of morbid and mortal events with an incidence of 203.56 events per 1,000 person-years. These findings point to the need for targeted interventions to identify and manage at-risk individuals.

## 7.2 Introduction

In Chapter 3, we conducted a systematic review of the incidence, prevalence and outcomes of rheumatic heart disease (RHD) in the new South Africa. Our review showed scanty contemporary data on the burden of RHD. One report determined the incidence of newly diagnosed RHD in individuals older than 14 years as 24.7 per 100,000 population, albeit associated with significant morbidity (Sliwa et al., 2010). A single echo-based prevalence study reported a prevalence of 20.2 per 1,000 schoolchildren screened (Engel, 2012). National cause-specific mortality rates are decreasing and the post-surgical prognosis appears to be favourable. However, in contrast, South African RHD patients presenting with acute heart failure have a 60-day mortality rate of 24.8% (95% CI 13.6 to 42.5) and a 180-day mortality of 35.4% (95% CI 21.6 to 54.4). The review highlighted the need for high-quality, systematically collected longitudinal data to quantify the outcomes of RHD in South Africa and to assess the prevailing prognostic factors associated with mortality and morbidity.

The Global Rheumatic Heart Disease Registry (The REMEDY study) is a prospective study of the incidence and prevalence of the sequelae, mortality and practice of evidence-based interventions in RHD. The baseline characteristics of the 3343 participants that were recruited from 14 countries have been reported recently (Zühlke et al, 2014). Here, I report the baseline characteristics and outcomes at 2-years of the 531 adults and children who were enrolled at Red Cross War Memorial Children's Hospital and Groote Schuur Hospital in Cape Town, South Africa.

## 7.3 Methods

The rationale, design and detailed methods of the REMEDY study are described in full in Section 2.3. of this thesis (Karthikeyan et al., 2012a): Ethics approval for the study is included in the appendix 10.1. This report describes the baseline characteristics, incidence of sequelae, and outcome of patients enrolled at two sites in Cape Town, South Africa, viz. Red Cross War Memorial Children's Hospital and Groote Schuur Hospital, over a 24-month period.

## 7.4 Results

### *Clinical characteristics*

A total of 531 participants were enrolled from the two sites between January 2010 and September 2012. They represented all age groups, with a median age of 46 years [IQR 35-58] and predominantly female (n=408, 76.8%). Just over half of these were of childbearing age (n=230, 56.4%). Adults between the ages of 18 and 65 were largely unemployed (n=288, 71.3%), however the majority of adults (n=348, 73.3%) had completed secondary schooling (Table 7.1; Figure 7.1).

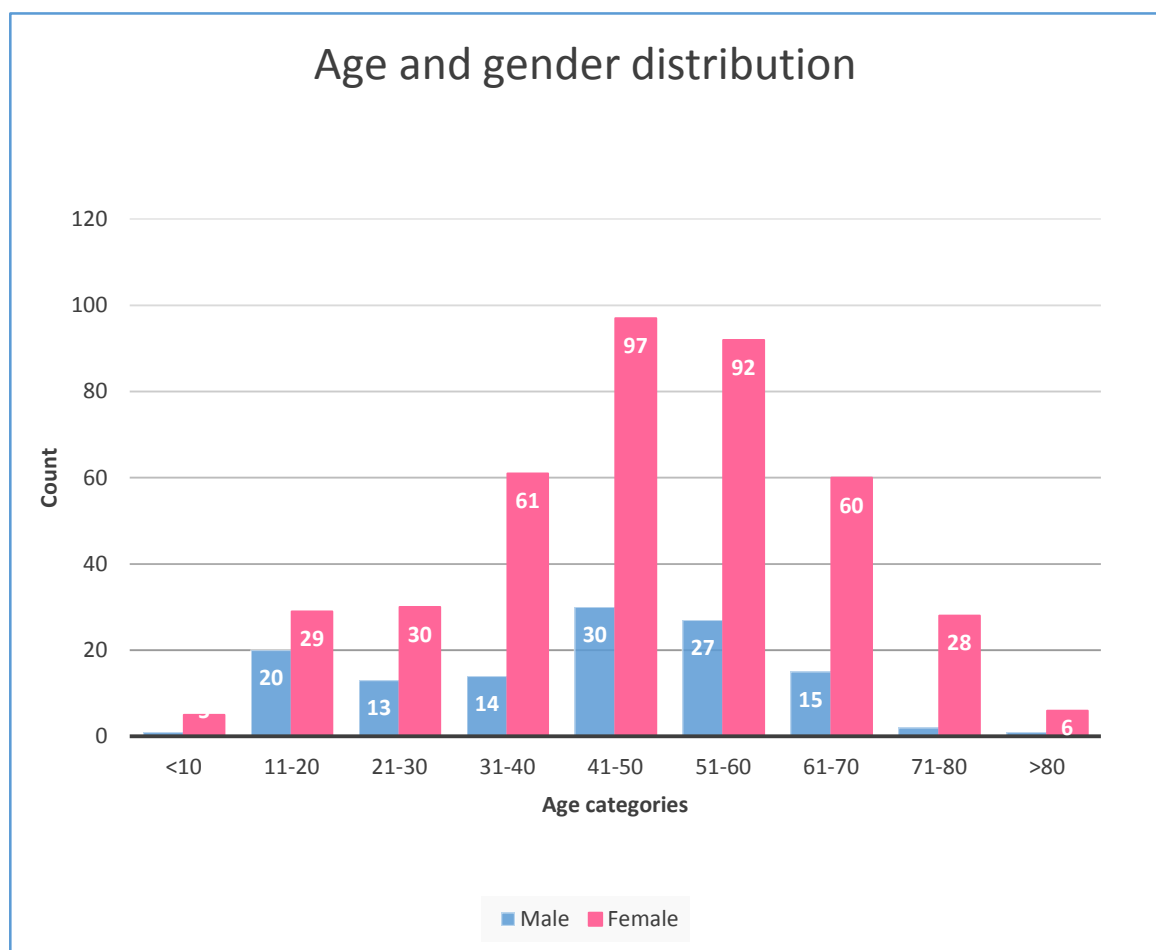


Figure 7.1. Age and gender distribution

Table 7.1. Baseline characteristics

	Red Cross Children's Hospital	Groote Schuur Hospital	Total
<b>Cases, N (%)</b>	42 (7.9)	489 (92.1)	531
<b>Female, N (%)</b>	26 (61.9)	382 (78.1)	408 (76.8)
<b>Time since diagnosis, yrs.; median (IQR)</b>	3.18 (0.8-7.3)	18.4 (7.1-31.7)	15.4 (5.7-30.5)
<b>Schooling lower than primary school level N, (%)*</b>		127 (26.7%)	127
<b>Unemployment N, (%) **</b>		351 (74.21)	351

Acronyms: N – numbers, IQR – Interquartile range;

\* Adults, \*\* adults 18-65 years

*Baseline clinical, past medical and surgical history and echocardiographic characteristics*

Fig. 7.2 shows the frequency of sequelae at the time of enrolment in the registry (baseline). There was substantial variation in the clinical features, past medical and surgical history, and baseline echocardiographic characteristics between the children and adults (Table 7.2). Not surprisingly, a history of stroke and cardiovascular complications in general was reported, albeit more frequently in adults (20.5% and 30.8% respectively) than in children (4.8% and 3.2% respectively) ( $P=0.008$ ). Children were, however, more likely to report a past history of ARF ( $n=40$ , 95.2%) compared to adults ( $n=343$ , 70.7%) ( $P=0.0001$ ). Seven percent of the cohort was in New York Heart Association (NYHA) functional class III-IV, while clinical signs of pulmonary hypertension was found in 19 cases (3.6%), pulmonary oedema in 16 cases (6.15%) and CCF in 22 cases (4.2%) on clinical examination. A quarter had decreased left ventricular ejection fraction ( $n=121$ , 25.9%) and dilated left ventricular end diastolic diameter (LVEDD) ( $n=122$ ,  $n=25.6\%$ ). Over 44.4% of children had a dilated LVEDD compared to 23.6% in adults ( $P=0.002$ ), while more adults had a decreased ejection fraction ( $n=117$ , 11.6%) compared to children ( $n=4$ , 3.3%) ( $P=0.007$ ). As expected, the use of valve replacement/repair and valvuloplasty was higher in adults than in children ( $P=0.001$ ). Among the post-surgery individuals, 77.8% of children and 85.2% of adults had had a valve replacement.



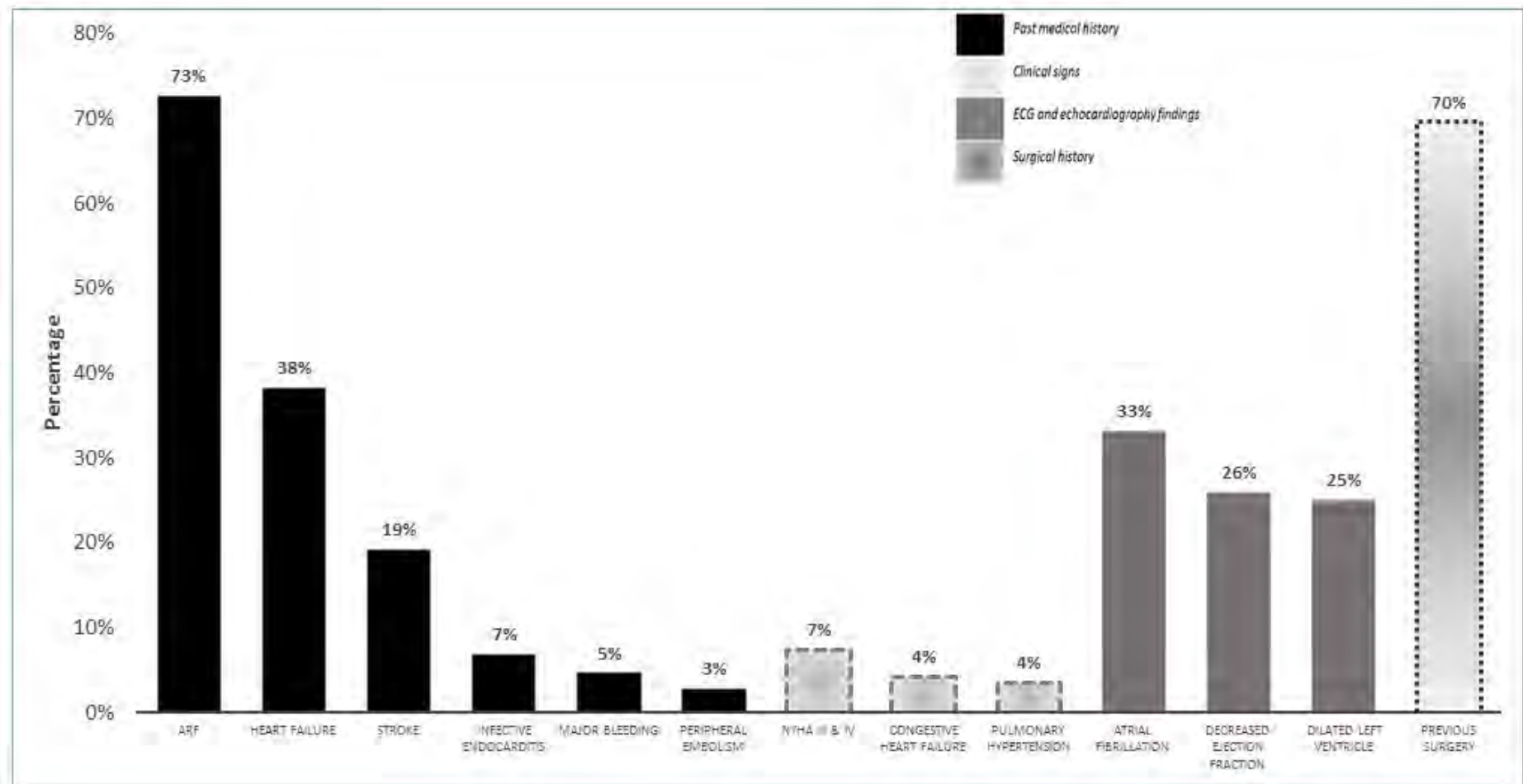
Table 7.2. Baseline clinical, past medical and surgical history and echocardiographic characteristics

Findings		Children N=52(9.8%)	Adults N=479(90.2%)	Total N=531 (%)	p
<b>Medical history</b>	Congestive cardiac failure	17 (32.7)	186 (39.0)	203 (38.4)	0.375
	Stroke	3 (5.8)	99 (20.8)	102 (19.3)	0.008
	Infective endocarditis	4 (7.7)	33 (6.9%)	37 (6.9)	0.775
	Major bleeding	-	25 (5.3)	25 (4.7)	
	Peripheral embolism	-	15 (3.2)	15 (2.9)	
	Complications*	7 (13.5)	148 (31.3)	155 (29.3)	0.008
	HIV positivity	0	20 (6.69)	20 (6.35)	
<b>Past medical history of Acute Rheumatic Fever</b>		48 (92.3)	335 (70.5)	383 (72.7)	<0.0001
<b>New York Heart Association Classification III and IV</b>		2(4.8)	37(7.6)	39 (7.4)	0.758
<b>Pulmonary hypertension</b>		3(5.7)	16(3.4)	19(3.6)	0.419
<b>Pulmonary oedema**</b>		3(11.5)	13(5.6)	16(6.15)	0.206
<b>Congestive cardiac failure</b>		6(14.3)	16(3.3)	22(4.2)	0.005
<b>Atrial Fibrillation**</b>		1 (3.3)	121(35.8)	122(33.2)	0.001
<b>Echocardiography</b>	Decreased ejection fraction	4 (3.3)	117 (11.6)	121 (25.9)	0.007
	Dilated left ventricle	20 (44.4)	102 (23.6)	122 (25.6)	0.002
	Dilated left atrium		110(22.5)	110(20.7)	
	Left atrial thrombus		3 (0.6)	3 (0.5)	
<b>Surgery</b>	Total	18(34.6)	352(73.8)	370(70.0)	
	Valve replacement	14 (63.7)	300 (85.1)	314 (69.9)	0.001
	Mechanical	14 (100)	282 (95.3)	296 (95.5)	0.001
	Bio-prosthesis		14 (4.7)	14 (4.5)	
	Combination		4 (1.3)	4 (1.3)	
	Valve repair	4(22.2)	52(14.9)	56(15.1)	0.001
	Replacement vs repair	14:4	300:52	314:56	0.496
Percutaneous valvuloplasty		3 (5.8)	62 (13)	65 (12.3)	0.001

\*Composite of stroke, Infective endocarditis, major bleeding and peripheral embolism.

\*\*Available data

Acronym: HIV – Human Immunodeficiency Virus.



Acronyms: ARF – Acute Rheumatic Fever; NYHA – New York Heart Association classification III & IV.

Figure 7.2. Findings on history and clinical examination

### *Follow-up*

The mean follow-up period was  $20.72 \pm 7.1$  months. Of the subjects, 77.6% completed an in-hospital visit at 12 months, and 76.5% at 24 months. There were nine patients with no further contact after enrolment, thus amounting to a lost-to-follow-up rate of 1.7%. The remainder of cases completed either a telephonic follow-up or a follow-up using hospital records. At the end of the study, the primary outcome status was known for 522 participants (98.3%).

### *Mortality*

Death occurred in 44 cases (8.3%) over the 24-month period. The crude-mortality rate is 4.15% per year or 42.7 per 1,000-person years. Figure 7.3 depicts the survival of the study patients in comparison with the general population matched for age, gender and ethnicity. The survival in this cohort was similar to the general population ( $P=0.98$ ). The mean age at death was 53.8 years ( $\pm 16.4$ , minimum 13, maximum 80 years). There were two children (mean age at death  $15.7 \pm 0.98$  years) and 42 adults (mean age at death  $56.9 \pm 14.32$  years) who died in this study. The causes of death were largely unknown ( $n=31$ , 70.5%). There were four sudden deaths (9.2%), four deaths from pneumonia (9.2%), two from prosthetic valve thrombosis (4.6%), and one death each from cardiogenic shock (2.2%), bronchospasm (2.2%) and complete heart block (2.2%).

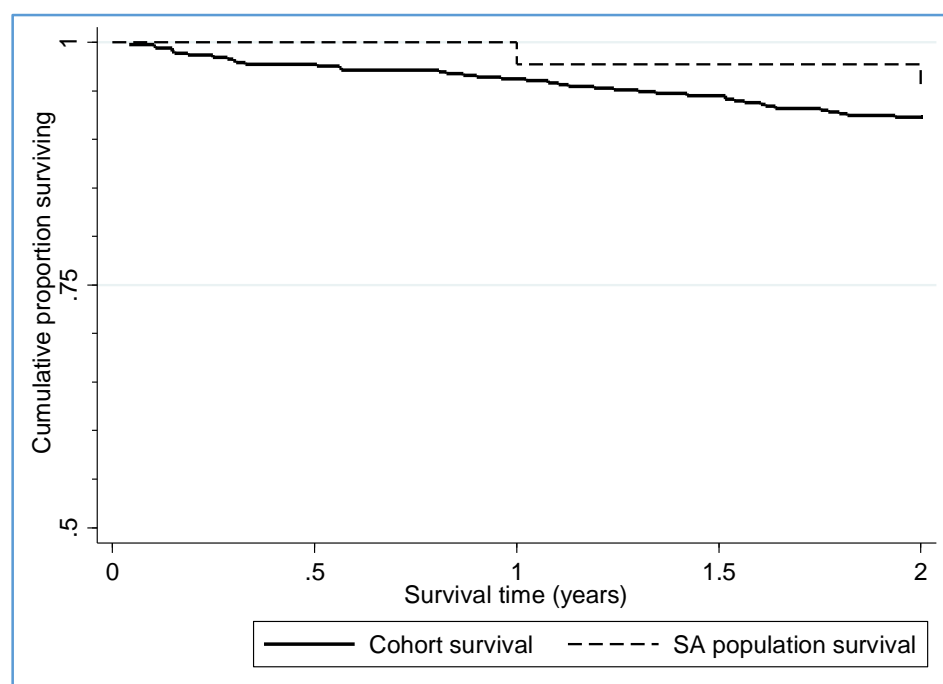


Figure 7.3. Kaplan-Meier survival analysis of study patients compared to match population controls

*Predictors of mortality*

In univariable Cox regression analyses, a history of CCF (hazard ratio 2.73, 95% CI 1.49 to 5.03,  $P=0.001$ ) and NYHA functional class III-IV (hazard ratio 3.78, 95% CI 1.74 to 8.18,  $P=0.001$ ) was associated with increased hazard of death. Additional predictors on univariable analysis were clinical findings of pulmonary oedema (hazard ratio 4.09, 95% CI 1.37 to 12.15,  $P=0.011$ ), CCF (hazard ratio 6.48, CI 2.72 to 15.38,  $P<0.0001$ ) and atrial fibrillation (AF) (hazard ratio 2.79, 95% CI 1.33 to 5.85,  $P=0.006$ ). A decreased ejection fraction at enrolment was also associated with increased hazard of death (hazard ratio 2.76, 95% CI 1.56 to 4.9,  $P=0.001$ ) (Figure 7.4). In contrast, only use of secondary prophylaxis conferred a decreased risk (hazard ratio 0.31, 95% CI 0.09 to 0.99,  $P=0.049$ ).

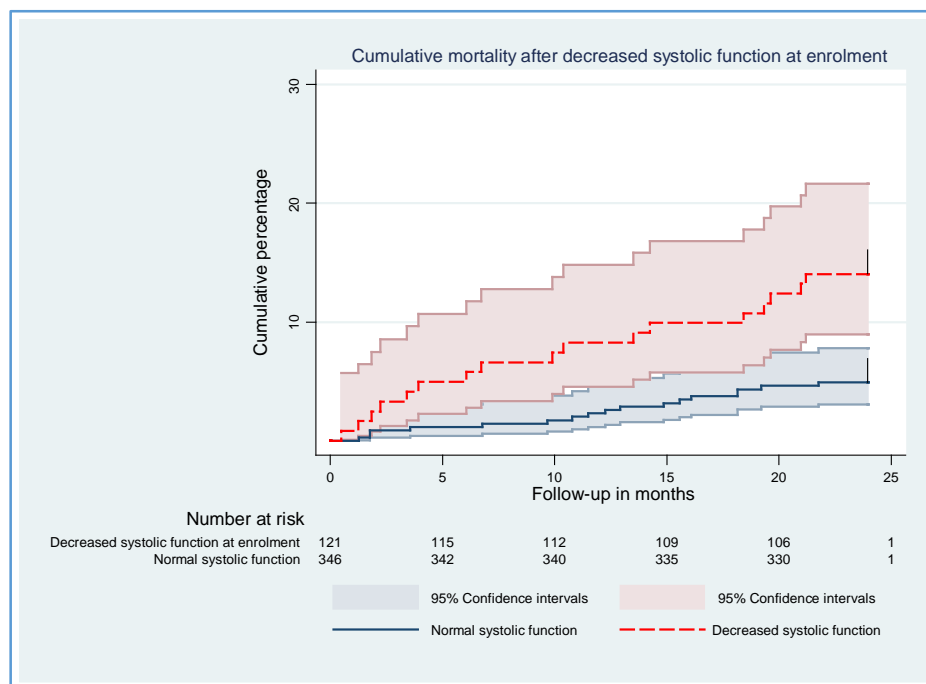


Figure 7.4. Cumulative mortality with decreased ejection fraction at enrolment

In the multivariable Cox regression model, the association with clinical congestive cardiac failure (hazard ratio 41.9, 95% CI 7.37 to 238.14,  $P<0.0001$ ), pulmonary oedema at enrolment (hazard ratio 5.91, 95% CI 1.21 to 28.75,  $P=0.028$ ) and decreased enrolment left ventricular ejection fraction (hazard ratio 16.8, 95% CI 3.23 to 87.45,  $P=0.001$ ) remained significant and independent predictors of mortality.

Table 7.3. Univariable and multivariable models for all-cause mortality

Enrolment predictors		Univariable model		Multivariable model*	
		Hazard ratio ( 95% CI)	P- value	Hazard ratio ( 95% CI)	P-value
<b>Female gender</b>		0.6 (0.33-1.18)	0.15		
<b>Past Medical history</b>	Congestive cardiac failure	2.73 (1.49-5.03)	0.001	1.38 (0.39-4.87)	0.61
	Stroke	1.73 (0.89-3.39)	0.12		
	Infective endocarditis	1.14 (0.35-3.67)	0.83		
	Major bleeding	0.95 (0.22-3.9)	0.94		
	Peripheral embolism	0.85 (0.18-6.19)	0.85		
	Complications	1.73 (0.94-3.19)	0.08		
	HIV positive	1.9 (0.44-8.23)	0.39		
<b>Past medical history of ARF</b>		0.55 (0.30-1.01)	0.05		
<b>NYHA III and IV</b>		3.78 (1.74-8.18)	0.001	0.36 (0.6-2.29)	0.28
<b>Pulmonary hypertension</b>		3.14 (0.97-10.15)	0.06		
<b>Pulmonary oedema</b>		4.09 (1.37-12.15)	0.011	5.91 (1.21-28.75)	0.028
<b>Congestive cardiac failure</b>		6.48 (2.72-15.38)	<0.0001	41.91 (7.37-2238.14)	<0.0001
<b>Atrial Fibrillation</b>		2.79 (1.33-5.85)	0.006	0.65 (0.17-2.44)	0.52
<b>Echocardiography</b>	Decreased ejection fraction	2.76 (1.56-4.90)	0.001	16.8 (3.23-87.45)	0.001
	Dilated left ventricle	1.07 (0.58-1.84)	0.90		
	Left atrial thrombus	4.21 (.58-30.69)	0.16		
<b>Percutaneous valvuloplasty</b>		1.17 (0.49-2.75)	0.73		
<b>Previous surgery</b>		1.32 (.65-2.67)	0.44		
<b>On secondary prophylaxis</b>		0.31 (0.09-0.99)	0.049	1.9 (0.01-36.1)	0.67
<b>On anticoagulant therapy</b>		1.43 (0.66-3.08)	0.36		
<b>On Warfarin</b>		1.94 (0.87-4.37)	0.11		

Acronyms: ARF – Acute Rheumatic Fever; NYHA – New York Heart Association classification III & IV.

*Cardiovascular events*

Cardiovascular complications occurred in 124 subjects (23.3%) or 11.7%/yr. In total, there were 187 events during the 24-month period (203.56 per 1,000 person-years) (Table 7.4).

Table 7.4. Cardiovascular events and interventions

Post-enrolment events		Children	Adults	Total n	P	%/yr.	Event – per 1,000 person years
<b>Cardiovascular Complications</b>	Congestive cardiac failure	2	39	41	0.382	3.86	40.5
	Major bleeding	0	15	15	0.381	1.41	14.3
	Stroke	1	14	15	1	1.41	14.3
	PVT -mechanical valves	3	6	9	0.049	0.85	8.5
	Atrial fibrillation	0	8	8	1	0.75	7.6
	Infective endocarditis	1	3	4	0.339	0.38	3.8
	Acute rheumatic fever	3	1	4	0.003	0.38	3.8
	Systemic embolism	0	1	1	1	0.09	0.9
<b>Total</b>		20	167	187	0.52	11.7	203.56
<b>Hospitalisation</b>		14	132	146	0.92	13.2	164.5
<b>Surgery</b>	Replacement/ repair	8	37	45	0.06	4.24	45.86
	Percutaneous valvuloplasty		1	1	1.0	0.09	0.9
<b>Pregnancy</b>		2	10	12	0.336	1.5	
<b>Deaths</b>		2	42	44	0.295	4.15	43.1

*PVT, prosthetic valve thrombosis*

*Mortality related to development of complications*

We depict univariable and multivariable models of death associated with development of adverse cardiovascular events in Table 7.5. Three cardiovascular events were associated with an increased hazard of death in a multivariable model, congestive heart failure (hazard ratio 7.66, 95% CI 5.89 to 16.37,  $P<0.001$ ), stroke (hazard ratio 5.61, 95% CI 1.82 to 17.29,  $P=0.003$ ) and prosthetic valve thrombosis (hazard ratio 8.16, 95% CI 1.48 to 44.96,  $P=0.016$ ).

Table 7.5. Models for adverse cardiovascular events and all-cause death

Cardiovascular Events as predictors	Univariable model		Multivariable model	
	Hazard ratio ( 95% CI)	P-value	Hazard ratio ( 95% CI)	P-value
Congestive cardiac failure	11.1 ( 5.6-21.96)	0.000	7.66 (3.589 -16.37)	<0.0001
Stroke	7.82 (3.19019.13)	0.000	5.61 (1.82-17.29)	0.003
Prosthetic Valve Thrombosis	13.01 (5.07-33.4)	0.000	8.16 (1.48-44.96)	0.016
Surgery	3.98 (1.59-9.95)	0.003	2.54 (0.87-7.38)	0.087
Atrial Fibrillation	8.69 (2.65-028.41)	0.000	1.05 (0.15-7.15)	0.96
Major bleeding	4.84 (1.66-14.10)	0.004	1.33 (0.36-4.86)	0.67
Systemic embolism	29.7 (3.95-223.06)	0.001	5.8 (0.45-74.27)	0.18
Infective endocarditis	3.16 (0.35-28.46)	0.304		
Acute Rheumatic Fever	No deaths			
Valvuloplasty	No deaths			

The overall multivariable model for all-cause mortality including enrolment and subsequent factors demonstrated that the highest risk of mortality was among those who were in CCF at the time of enrolment (hazard ratio 15.73, 95% CI 3.94 to 62.7,  $P<0.0001$ ). Decreased ejection fraction at the time of enrolment was thus an additional independent factor for increased risk. New episodes of CCF conferred the highest associated risk with mortality (hazard ratio 11.1, 95% CI 5.6 to 21.96,  $P=0.047$ ), while stroke remained associated with increased mortality risk (hazard ratio 7.84, 95% CI 3.19 to 19.13,  $P=0.022$ ) in the multivariable model (Table 7.6).

Table 7.6. Models for all-cause mortality: Enrolment and subsequent variables

Morbid predictors Enrolment and subsequent events	Univariable model		Multivariable model	
	Hazard ratio ( 95% CI)	P-value	Hazard ratio ( 95% CI)	P-value
Congestive cardiac failure at enrolment	2.73 (1.49-5.03)	0.001	15.73 ( 3.94-62.7)	<0.0001
Decreased ejection fraction at enrolment	2.76 (1.56-4.90)	0.001	5.93 (1.88-18.7)	0.002
Pulmonary oedema at enrolment	4.09 (1.37-12.15)	0.011	3.45 (0.91-13.07)	0.069
New congestive cardiac failure episode	11.1 ( 5.6-21.96)	0.000	3.8 1.02-14.48)	0.047
New stroke episode	7.82 (3.19 to 19.13)	0.000	6.59 (1.3-33.1)	0.022

*Cardiac failure at enrolment and subsequent episodes of cardiac failure*

The mortality rate for subjects enrolled in cardiac failure was 3.63% (95% CI 1.72 to 59.3%), compared to those not in cardiac failure at the time of enrolment 0.7% (95% CI 0.5 to 0.95%), log-rank test  $P=0.0001$  (Figure 7.5). The mortality rate for those developing an episode of cardiac failure was 24.3% (95% CI 12.3 to 40.3%) compared to 6.33% (95% CI 4.33 to 8.86%), log-rank test  $P<0.0001$ , among those without any episodes of cardiac failure during the follow-up period. Figure 7.6 depicts the comparison of cumulative mortality with 95% confidence intervals.



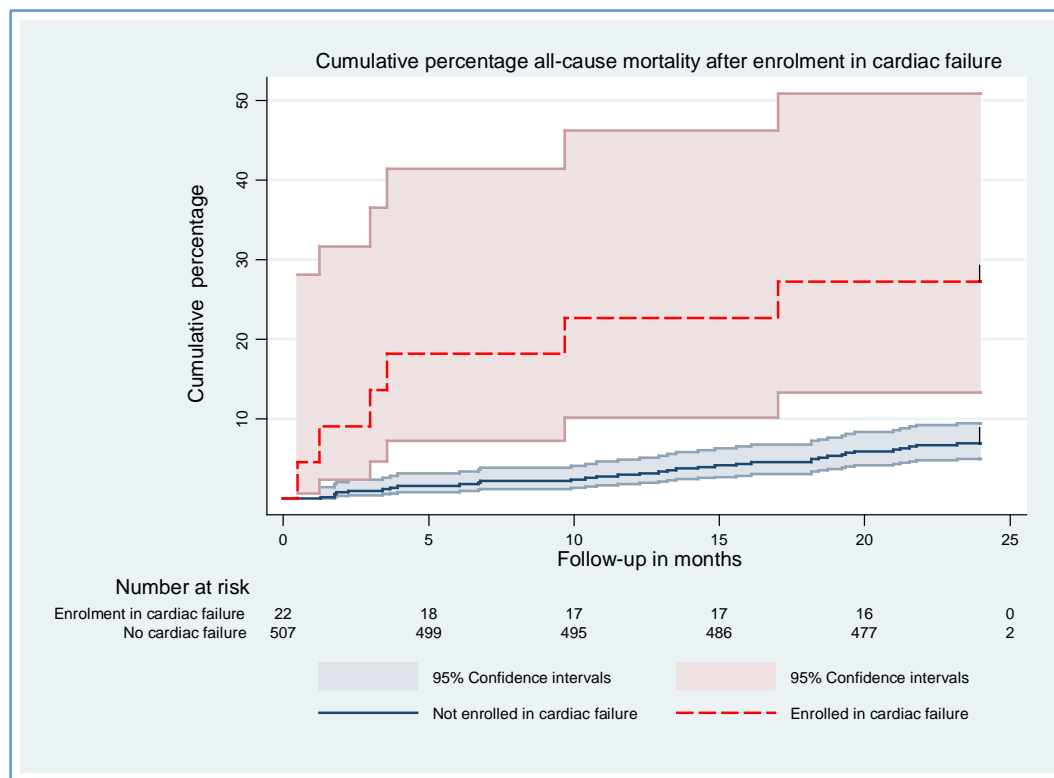


Figure 7.5. Cumulative mortality after cardiac failure at enrolment

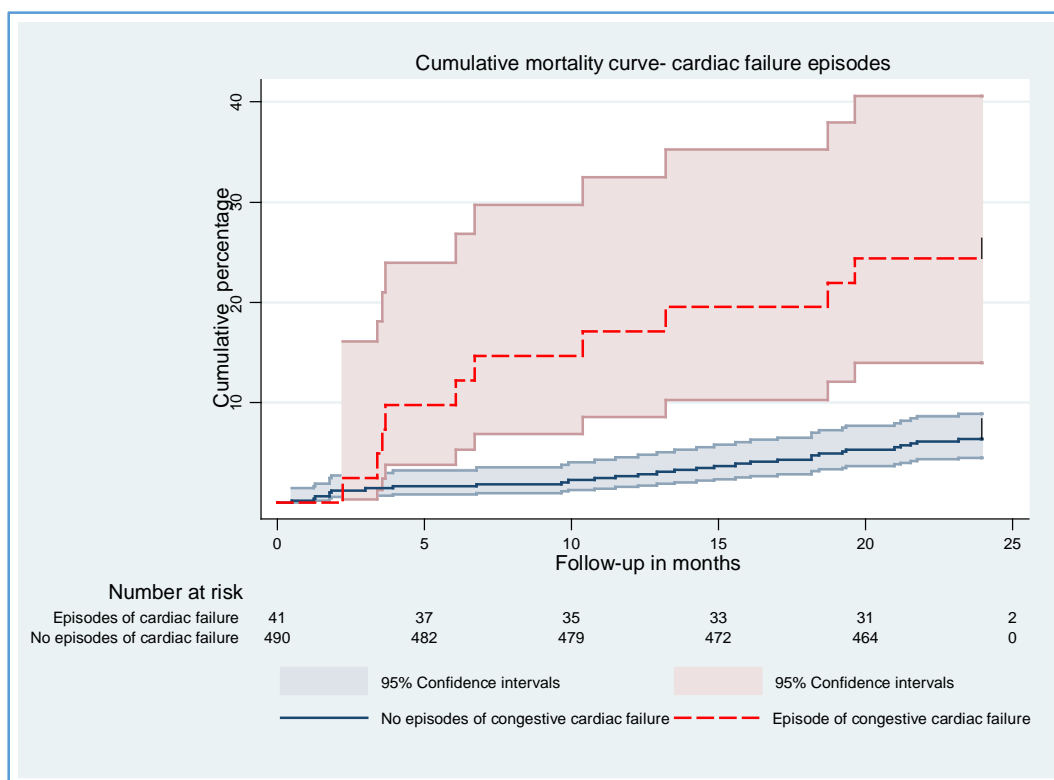


Figure 7.6. Comparison of cumulative percentage all-cause mortality for those with or without episodes of cardiac failure

*Morbidity: Adverse cardiovascular events*

Patients with previous complications were more likely to experience another cardiovascular event (39.3% versus 25.8%,  $P=0.004$ ). The most common complications over the 24-month period were congestive heart failure (3.7%/yr.), stroke (1.42%/yr.) and bleeding (1.33%/yr.). New congestive heart failure was associated with a NYHA functional class of III-IV (hazard ratio 4.9, 95% CI 1.85 to 11.8,  $P<0.0001$ ), clinical CCF (HR 4.4, 95% CI 1.54 to 12.3,  $P=0.005$ ) and decreased left ventricular ejection fraction (hazard ratio 2.16, 95% CI 1.0 to 4.57,  $P=0.02$ ) at enrolment. A positive HIV status was not a predictor of CCF (HIV positive 15% versus HIV negative 6.5%,  $P=0.16$ ). On multivariate analysis and adjusting for age and gender, subjects with a NYHA functional class of III-IV at enrolment were 6.25 more likely to develop another episode of heart failure during the subsequent 24 months than those in lower functional classes at enrolment (hazard ratio 3.25, 95% CI 1.1 to 9.5,  $P=0.032$ ).

There were 15 new cases of stroke over 2 years (1.42%/yr.). A left atrial thrombus at enrolment (33.3% versus 2.56%,  $P=0.0001$ ) was associated with increased risk of stroke during the subsequent 24 months (HR 25.1, 95% CI 3.0 to 208.6,  $P=0.003$ ).

*Native valves*

At baseline, just over three-quarters of the subjects were post-surgical or post-percutaneous intervention (392/531, 73.8%). These subjects were less likely to present with CCF (1.8% vs. 10.8%,  $P<0.0001$ ). However, post-intervention subjects had more systolic dysfunction at enrolment (29% vs. 18.2%,  $P=0.017$ ). There were no statistical differences in pulmonary oedema at enrolment, development of new episodes of CCF or stroke, nor overall mortality (Table 7.7).

Table 7.7. Previously identified independent risk factors: Pre and post-intervention comparison

	<b>Native Valves n (%)</b> <b>N=139 (26.2%)</b>	<b>Post-intervention n (%)</b> <b>N=392 (73.8%)</b>	<b>P-value</b>
Congestive cardiac failure at enrolment	15 (10.8)	7 (1.8)	<0.0001
Decreased ejection fraction at enrolment	24 (18.2)	97 (29)	0.017
Pulmonary oedema at enrolment	8 (10.53)	8 (4.35)	0.059
New congestive cardiac failure episode	11 (7.65)	30 (7.65)	0.921
New stroke episode	2 (1.4)	13 (3.3)	0.251
Any event	39 (28.1)	85 (21.68)	0.127
All-cause death	9 (6.47)	35 (8.93)	0.367

## 7.5 Discussion

Three key findings emerge from this report of contemporary prospectively collected outcomes of symptomatic RHD in South Africa. Firstly, we report an annual mortality rate of 4.1% that is strongly associated with symptomatic cardiac failure, decreased left ventricular ejection fraction or pulmonary oedema on chest x-ray at enrolment or a subsequent episode of CCF, stroke or prosthetic valve thrombosis. Secondly, we describe a cohort of predominantly RHD survivors, with almost a third having a history of previous cardiovascular events and almost three-quarters having undergone surgery or valvuloplasty. Yet, we demonstrate a significant event rate of 203.56 per 1,000 person-years. Finally, development of the most common complications, namely, congestive heart failure, stroke and bleeding is associated with a NYHA functional class of III - IV, presence of left atrial thrombi, AF and use of anticoagulation.

South Africa is an upper middle-income country with tremendous resources alongside persisting inequalities (Mayosi and Benatar, 2014). In the baseline report of findings from countries in Africa, India and Yemen, we reported on observed variations in cardiovascular complications, AF, left ventricular dysfunction and the use of percutaneous and surgical intervention by country income status (Zühlke et al., 2014a). The tertiary institutions in this study drain the uninsured indigent, population of the Western Cape Province and surrounding areas (Buchanan-Leel et al., 2002; Geldenhuys et al., 2012), yet demonstrate a high prevalence of pre-existing cardiovascular sequelae

and significant use of surgical and percutaneous interventions, as reported from another upper-middle incomes site in our study. These patients thus largely represent survivors of RHD with significantly lower rates of baseline clinical pulmonary hypertension (3.4% vs 28.6%) and CCF (4.2% vs 33.2%) compared to the total cohort.

The annual mortality rate for RHD varies from 1.25% to 12.5% (Carapetis et al., 2005; Gunther et al., 2006). We report an annual all-cause mortality rate of 4.1%. This is associated with a history of CCF and a decreased ejection fraction (EF) at enrolment and the incidence of cardiac failure, stroke and prosthetic valve thrombosis (PVT) during follow-up. We have previously reported on the high 60- and 180-day mortality rate associated with acute heart failure in RHD in a South African population of 24.8 and 35.4% respectively (Chapter 3). The mortality rate in this cohort, for subjects enrolled in cardiac failure was 3.63% (95% CI 1.72 to 59.3%) and 24.3% (95% CI 12.3 to 40.3%) for those developing an episode of cardiac failure during the study period. Heart failure is emerging as an important form of cardiovascular disease in Africa, with non-ischaemic causes such as RHD and hypertension remaining predominant (Ntusi and Mayosi, 2009). RHD has been shown to be a prognostic indicator of mortality in children with heart failure (Omokhodion and Lagunju, 2005), whilst admission with heart failure is associated with significant mortality in RHD globally (Parks et al., 2014). Targeted therapeutic interventions for patients with RHD presenting with or developing cardiac failure should be a priority.

We also report on the survival of our subjects compared to the national life tables. Even after matching for age, ethnicity and gender, there are no considerable differences between people with RHD and the South African general population. Yet, this comparison is of interest, especially since (Statistics SA's Mortality and Causes of Death in South Africa Report for 2011, 2014), the overall life expectancy at birth of the South African population was only 60 years in 2012 (Mayosi and Benatar, 2014).

Development of the most common complications, namely congestive heart failure, stroke and bleeding, was associated with a NYHA functional class of III-IV, presence of left atrial thrombi, AF and use of anticoagulation. These outcomes are consistent with two recent South African surgical reviews with follow-up periods of five and 10 years (Barnard et al., 2010; Geldenhuys et al., 2012). The incidence rate of adverse cardiovascular events related to RHD of 203.56 (95% CI 177.9 to 230.98) per 1,000-person years reflects a heavy burden of disease in a relatively young population. Nevertheless, this finding is consistent with high number of events in other studies

(Damasceno et al., 2012; Healey et al., 2011). Sliwa et al. demonstrated that surgery was performed in 22% of their cohort and that 26% were admitted within 30 months of initial diagnosis for suspected bacterial endocarditis (Sliwa et al., 2010). There is thus clearly a need to identify factors leading to these high rates of events.

#### *Implications for practice*

Our data confirms that this cohort of RHD patients remains at risk of mortality and morbidity. A more vigilant medical and surgical approach is required to reduce the high morbidity and mortality that has been found. We have previously (Chapter 6) demonstrated significant gaps in the use of evidence-based medical and surgical interventions in these patients, such as penicillin for secondary prophylaxis, oral anticoagulation, percutaneous and surgical strategies. A clear target should be patients with heart failure due to RHD, who require full pharmacological and surgical strategies to be employed, including cardiac transplantation (Chi et al., 2014; Lanza et al., 1984).

#### *Implications for research*

A recent study reported on the relationship between income categories, risk-factor burden and incident cardiovascular disease (Yusuf et al., 2014). Using a validated risk assessment score, they report a higher risk-factor burden in high-income countries but with lower rates of major cardiovascular disease and death. The cohort described in Study 5 of this thesis is embedded within the REMEDY study, with 3,343 patients from countries that fall into three income groups. This is the ideal base to derive a risk-stratification score, using generalised linear modelling with time-varying covariates for patients with RHD. This study will be undertaken once the REMEDY follow-up period is complete. Prognostic indicators and predictors for Adverse Cardiovascular Events associated with RHD (PACER) should aid in the identification and recognition of patients at particular risk. Studies investigating the costs of care for RHD survivors are scant and are also needed to provide important health policy information.

Our study has several limitations. Despite all our efforts, we have a 1.7% loss-to-follow-up. In addition, over a quarter of patients did not attend their follow-up clinic appointment. However, efforts were made to review the documentation of all events, and, where possible, all death certificates were reviewed. A history of previous complications was taken on enrolment which may be prone to error. However, hospital records were scrutinised to verify the historical information

as far as possible. RHD is a chronic disease, which requires more than twenty-four months of observation to establish the frequency and determinants of outcome. Our data show a predominance of valve replacement, which may only develop complications 10 to 15 years post-surgery. Therefore, longer-term studies of focused interest subpopulations are needed to elucidate these outcomes. Our patients were largely post-interventional survivors and thus our findings cannot be extrapolated to newly diagnosed patients, who have been shown to have significantly different outcomes (Okello et al., 2013). Finally, patients with subclinical outcomes, such as intermittent arrhythmias or transient ischemic attacks, may not be presenting to health care centres, and undiagnosed episodes of ARF are likely to have occurred during the follow-up period.

## **7.6 Conclusion**

RHD patients enrolled in the tertiary institutions in Cape Town are predominantly female and largely post-surgical, with a high prevalence of complications at enrolment. Over a period of 24 months, we documented an annual mortality rate of 4.1%, which is strongly associated with cardiac failure at enrolment and subsequent episodes of cardiac failure. There is a heavy burden of morbid and mortal events with an incidence of 203.56 events per 1,000 person-years. Targeted interventions are urgently needed to identify and manage at-risk individuals, especially with acute heart failure and decreased systolic function.

## 8 Summary and conclusions

This thesis incorporated five linked studies to explore critical questions regarding the outcomes of asymptomatic and symptomatic rheumatic heart disease (RHD). This summary chapter lists the unique contributions made by these studies, presents implications for both policy and practice, and makes recommendations for future research.

### 1. Principal findings

The primary purpose of the thesis was to determine the outcomes of asymptomatic and symptomatic RHD. More specifically, I sought to quantify the incidence, prevalence and outcomes of RHD in South Africa over the past two decades, determine the natural history of asymptomatic RHD and validate a focused protocol for screening in schoolchildren from Cape Town. In addition, I determined the baseline characteristics, prevalent sequelae and gaps in evidence-based implementation in children and adults from 14 developing countries.. Finally, I investigated the independent predictors for mortality and morbidity of RHD over a two-year period in patients from Cape Town, South Africa.

There are five principal findings from this series of studies. Firstly, mortality rates due to RHD on a population level are showing early signs of declining, while RHD patients have an excellent prognosis after surgical intervention. However, both prevalence and incidence rates remain high, while *de novo* cases of RHD are presenting with significant clinical disease. In particular, patients hospitalised with acute heart failure due to RHD have a significant rate of mortality.

Secondly, this thesis demonstrates that asymptomatic RHD as defined by the World Heart Federation (WHF) criteria is a dynamic condition that may regress, persist or progress to symptomatic disease over five years of follow-up. This work also showed the difference in the natural history of definite and borderline RHD, with no case of definite RHD reverting to a normal state. The presence of pathological MR was also confirmed as a strong predictor of persistent or progressive disease.

Thirdly, having demonstrated that pathological mitral regurgitation and definite disease are predictors of persistence, we present FOCUS, (FOCused method Utilizing hand-held echocardiography in Screening for rheumatic heart disease), a simple, short, sensitive and highly

specific method of screening for rheumatic heart disease incorporating hand-held ultra-portable echocardiography and a single criterion. Our data suggest that this method may be appropriate for the detection of definite rheumatic heart disease in resource-poor settings. The sensitivity of hand-held echocardiography is higher for definite rheumatic heart disease compared to borderline status. However, computer-assisted auscultation, tested here for the first time in this setting, is not a suitable screening modality for asymptomatic rheumatic heart disease due to extremely low sensitivity.

The fourth important finding is the quantification of the gaps in the implementation of medical and surgical interventions of proven effectiveness for RHD in low- and middle-income countries. These include inadequate use of penicillin for secondary prophylaxis, poor control of oral anticoagulant therapy, extremely low use of contraception in women with RHD, and insufficient access to percutaneous and surgical interventions by individual countries and the international community.

The fifth and final finding is the high burden of mortal and morbid events related to RHD in South Africa. The mortality rate of 4.1% per annum in contemporary South African patients is more than 3 times higher than that utilised in estimates of the global burden of disease by Carapetis et al in 2005. Cardiac failure and decreased systolic fraction at baseline and subsequent episodes of cardiac failure are predictors of subsequent events and mortality with an incident rate of 204 events per 1,000 person-years under observation.

## **2. Implications for policy and practice**

The findings of this thesis have important clinical implications. Firstly, patients with acute heart failure due to RHD are at a high risk for death, and require consideration for definitive therapy such as surgical intervention. The high mortality rate associated with heart failure due to RHD is a clarion call for early surgical intervention in these cases. Furthermore, the excellent prognosis post-surgery for RHD emphasises the necessity of access to these life-saving interventions in developing countries.

Secondly, a diagnosis of asymptomatic RHD on echocardiography requires confirmation in follow-up studies due to the dynamic nature of the condition – which may resolve, persist or deteriorate. This work suggests a minimum period of follow-up of 5 years to identify those who develop episodes of ARF and symptomatic RHD and require management according to evidence-based



standard guidelines. We recommend the establishment of secondary prevention registers in RHD-endemic communities to track both asymptomatic and symptomatic individuals. This is especially prudent, given the findings of our natural history study, which confirms the need for long-term follow-up.

Thirdly, this thesis highlights the need for contextually relevant screening programmes, which allow for integration within existing RHD and other primary health care control programmes, with an understanding of the outcomes of programmes. A simple, short, sensitive and highly specific method of screening for rheumatic heart disease that is suited to low-income settings, such as presented in this thesis, can be aligned with integrated models of care, where rheumatic heart disease could form one of the diseases easily screened for and managed by primary care teams.

Fourthly, these data call for strict adherence to guidelines for secondary prophylaxis, targeted reproductive services for women with RHD, improved monitoring and use of oral anticoagulation therapy. Moreover, these data emphasize the need for low and middle-income countries to have access to percutaneous and surgical interventions.

Finally, a more vigilant approach is required to reduce the high morbidity and mortality found in the Cape Town cohort. We need to address the gaps in evidence-based medical and surgical interventions with a clear target being patients with heart failure, who require full pharmacological and surgical strategies to be employed.

### **3. Implications for future research**

Each of the studies within this thesis has identified important areas of future research. Firstly, there is a clear requirement to establish the incidence, prevalence and temporal trends of RHD in South Africa through appropriately designed sentinel studies that will be generalizable to the whole population. The existence of the mandatory notification system for ARF and the proposed reporting of the first diagnosis of RHD provides the basis for the establishment of a national surveillance system for the disease. These could be combined with a management registry, which we anticipate could improve patient outcomes.

Secondly, the evidence of the persistence of definite disease in asymptomatic populations justifies longer-term studies to determine whether antibiotic prophylaxis is efficacious and cost-effective in

preventing the progression of asymptomatic RHD to symptomatic disease. There is a need for a large randomised controlled trial of antibiotic prophylaxis to determine the efficacy and cost-effectiveness of secondary prevention in asymptomatic RHD.

Thirdly, simple and reproducible tools for screening, such as FOCUS proposed and validated in this thesis, need further large-scale studies, including components of cost-effectiveness, training and acceptability analyses.

The fourth implication for further research is highlighted by the findings of the high mortality due to RHD and heart failure. The inclusion of RHD patients in trials for heart failure, atrial fibrillation and therapeutic interventions should be strongly encouraged. Economic modelling for interventions, particular around surgery is needed.

Finally, further studies to identify prognostic indicators and predictors for adverse cardiovascular events associated with RHD should aid in the recognition of patients at particular risk. In addition, there is a need for longer-term studies of targeted subpopulations, such as those post-intervention to elucidate outcomes. Studies into costs of care for RHD survivors are scarce; these will provide important health policy information.

In conclusion, the findings of this thesis have addressed key questions regarding the outcomes of asymptomatic and symptomatic RHD. We anticipate that it will set the scene for further comprehensive studies of asymptomatic and symptomatic RHD while providing key datasets to affect and influence policy.

## 9 References

- AGARWAL, A. K., YUNUS, M., AHMAD, J. & KHAN, A. 1995. Rheumatic heart disease in India. *Journal of the Royal Society of Health*, 115, 303-4, 309.
- AKINWUSI, P. O., PETER, J. O., OYEDEJI, A. T. & ODEYEMI, A. O. 2013. The new face of rheumatic heart disease in South West Nigeria. *Int J Gen Med*, 6, 375-81.
- AKOBENG, A. K. 2007. Understanding diagnostic tests 2: likelihood ratios, pre- and post-test probabilities and their use in clinical practice. *Acta Paediatr*, 96, 487-91.
- ANABWANI, G. M. & BONHOEFFER, P. 1996. Prevalence of heart disease in school children in rural Kenya using colour-flow echocardiography. *East Afr Med J*, 73, 215-7.
- ANTUNES, M. J. 1992. Valvuloplasty for acquired mitral regurgitation. *Cardiovascular Journal of South Africa*, 3, 9-16.
- ANTUNES, M. J. 1997. Valve repair for the treatment of rheumatic mitral regurgitation. *Cardiovascular Journal of Southern Africa*, 87, C265-C272.
- ATATO-CARR, P., LENNON, D. & WILSON, N. 2008. Rheumatic fever diagnosis, management, and secondary prevention: a New Zealand guideline. *N Z Med J*, 121, 59-69.
- AZEVEDO, P. M., PEREIRA, R. R. & GUILHERME, L. 2012. Understanding rheumatic fever. *Rheumatol Int*, 32, 1113-20.
- BA-SADDIK, I. A., MUNIBARI, A. A., AL-NAQEEB, M. S., PARRY, C. M., HART, C. A., CUEVAS, L. E. & COULTER, J. B. 2011. Prevalence of rheumatic heart disease among school-children in Aden, Yemen. *Ann Trop Paediatr*, 31, 37-46.
- BARNARD, B. J., LE ROUX, P. J. & VAN WYK, H. W. J. 2010. Mitral valve replacement at Tygerberg Hospital: a 5 year follow-up. *SA Heart*, Summer 2010, 30-37.
- BARTER, D. M., AGBOOLA, S. O., MURRAY, M. B. & BARNIGHAUSEN, T. 2012. Tuberculosis and poverty: the contribution of patient costs in sub-Saharan Africa--a systematic review. *BMC Public Health*, 12, 980.
- BASSILI, A., ZAHER, S. R., ZAKI, A., ABDEL-FATTAH, M. & TOGNONI, G. 2000. Profile of secondary prophylaxis among children with rheumatic heart disease in Alexandria, Egypt. *East Mediterr Health J*, 6, 437-46.
- BEATON, A., OKELLO, E., LWABI, P., MONDO, C., MCCARTER, R. & SABLE, C. 2012. Echocardiography screening for rheumatic heart disease in Ugandan schoolchildren. *Circulation*, 125, 3127-32.
- BEATON, A., ALIKU, T., OKELLO, E., LUBEGA, S., MCCARTER, R., LWABI, P. & SABLE, C. 2014a. The utility of handheld echocardiography for early diagnosis of rheumatic heart disease. *J Am Soc Echocardiogr*, 27, 42-9.
- BEATON, A., OKELLO, E., ALIKU, T., LUBEGA, S., LWABI, P., MONDO, C., MCCARTER, R. & SABLE, C. 2014b. Latent rheumatic heart disease: outcomes 2 years after echocardiographic detection. *Pediatr Cardiol*, 35, 1259-67.
- BEATON, A., LU, J. C., ALIKU, T., DEAN, P., GAUR, L., WEINBERG, J., GODOWN, J., LWABI, P., MIREMBE, G., OKELLO, E., REESE, A., SHRESTHA-ASTUDILLO, A., BRADLEY-HEWITT, T., SCHEEL, J., WEBB, C., MCCARTER, R., ENSING, G. & SABLE, C. 2015. The utility of handheld echocardiography for early rheumatic heart disease diagnosis: a field study. *Eur Heart J Cardiovasc Imaging*.
- BENJAMIN, E. J., WOLF, P. A., D'AGOSTINO, R. B., SILBERSHATZ, H., KANNEL, W. B. & LEVY, D. 1998. Impact of Atrial Fibrillation on the Risk of Death: The Framingham Heart Study. *Circulation*, 98, 946-952.
- BETIGERI, V. M., BETIGERI, A. V., KARTHIKEYAN, B. & SUBBARAO, K. S. 2013. Rheumatic mitral stenosis associated with sinus venosus atrial septal defect and partial anomalous pulmonary venous return. *Gen Thorac Cardiovasc Surg*, Jul 30.
- BHAYA, M., PANWAR, S., BENIWAL, R. & PANWAR, R. B. 2010. High prevalence of rheumatic heart disease detected by echocardiography in school children. *Echocardiography*, 27, 448-53.
- BHAYA, M., BENIWAL, R., PANWAR, S. & PANWAR, R. B. 2011. Two years of follow-up validates the echocardiographic criteria for the diagnosis and screening of rheumatic heart disease in asymptomatic populations. *Echocardiography*, 28, 929-33.

- BLAND, E. F. & DUCKETT JONES, T. 1951. Rheumatic fever and rheumatic heart disease; a twenty year report on 1000 patients followed since childhood. *Circulation*, 4, 836-43.
- BONOW, R. O., CARABELLO, B. A., CHATTERJEE, K., DE LEON, A. C., JR., FAXON, D. P., FREED, M. D., GAASCH, W. H., LYTLE, B. W., NISHIMURA, R. A., O'GARA, P. T., O'ROURKE, R. A., OTTO, C. M., SHAH, P. M., SHANEWISSE, J. S., WRITING COMMITTEE, M. & AMERICAN COLLEGE OF CARDIOLOGY/AMERICAN HEART ASSOCIATION TASK, F. 2008. Focused update incorporated into the ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1998 Guidelines for the Management of Patients With Valvular Heart Disease): endorsed by the Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *Circulation*, 118, e523-661.
- BOSSUYT, P. M., REITSMA, J. B., BRUNS, D. E., GATSONIS, C. A., GLASZIOU, P. P., IRWIG, L. M., MOHER, D., RENNIE, D., DE VET, H. C., LIJMER, J. G. & STANDARDS FOR REPORTING OF DIAGNOSTIC ACCURACY, G. 2003. The STARD statement for reporting studies of diagnostic accuracy: explanation and elaboration. The Standards for Reporting of Diagnostic Accuracy Group. *Croat Med J*, 44, 639-50.
- BOTHA, J. S., SCHEFFER, C., LUBBE, W. W. & DOUBELL, A. F. 2010. Autonomous auscultation of the human heart employing a precordial electro-phonocardiogram and ensemble empirical mode decomposition. *Australas Phys Eng Sci Med*, 33, 171-83.
- BOUDOULAS, K. D., BORER, J. S. & BOUDOULAS, H. 2013. Etiology of valvular heart disease in the 21st century. *Cardiology*, 126, 139-52.
- BROWN, A., MCDONALD, M. I. & CALMA, T. 2007. Rheumatic fever and social justice. *Med J Aust*, 186, 557-8.
- BUCHANAN-LEEL, B., LEVETAN, B. N., LOMBARD, C. J. & COMMERTFORD, P. J. 2002. Fixed-dose versus adjusted-dose warfarin in patients with prosthetic heart valves in a peri-urban impoverished population. *J Heart Valve Dis*, 11, 583-92; discussion 593.
- BUNDRED, P. E. 1986. *The place of primary care in the prevention and control of rheumatic fever and rheumatic heart disease in Southern Africa*. MD Thesis, University of London, London.
- BURGER, E. H., VAN DER MERWE, L. & VOLMINK, J. 2007. Errors in the completion of the death notification form. *S Afr Med J*, 97, 1077-81.
- BURGER, E. H., GROENEWALD, P., BRADSHAW, D., WARD, A. M., YUDKIN, P. L. & VOLMINK, J. 2012. Validation study of cause of death statistics in Cape Town, South Africa, found poor agreement. *J Clin Epidemiol*, 65, 309-16.
- CALDAS, A. M., TERRERI, M. T., MOISES, V. A., SILVA, C. M., CARVALHO, A. C. & HILARIO, M. O. 2007. The case for utilizing more strict quantitative Doppler echocardiographic criterions for diagnosis of subclinical rheumatic carditis. *Cardiol Young*, 17, 42-7.
- CARABELLO, B. A. 2005. Modern management of mitral stenosis. *Circulation*, 112, 432-7.
- CARAPETIS, J. R., CURRIE, B. J. & GOOD, M. F. 1996. Towards understanding the pathogenesis of rheumatic fever. *Scand J Rheumatol*, 25, 127-31; discussion 132-3.
- CARAPETIS, J. R., CURRIE, B. J. & MATHEWS, J. D. 2000. Cumulative incidence of rheumatic fever in an endemic region: a guide to the susceptibility of the population? *Epidemiology and infection*, 124, 239-44.
- CARAPETIS, J. R., STEER, A. C., MULHOLLAND, E. K. & WEBER, M. 2005. The global burden of group A streptococcal diseases. *The Lancet Infectious Diseases*, 5, 685-694.
- CARAPETIS, J. R. 2007. Rheumatic heart disease in developing countries. *N Engl J Med*, 357, 439-41.
- CARAPETIS, J. R. 2008. Rheumatic Heart Disease in Asia. *Circulation*, 118, 2748-2753.
- CARAPETIS, J. R., HARDY, M., FAKAKOVIAETAU, T., TAIB, R., WILKINSON, L., PENNY, D. J. & STEER, A. C. 2008. Evaluation of a screening protocol using auscultation and portable echocardiography to detect asymptomatic rheumatic heart disease in Tongan schoolchildren. *Nat Clin Pract Cardiovasc Med*, 5, 411-7.
- CARAPETIS, J. R. & ZÜHLKE, L. J. 2011. Global research priorities in rheumatic fever and rheumatic heart disease. *Ann Pediatr Cardiol*, 4, 4-12.

- CHI, N. H.,CHOU, N. K.,YU, Y. H.,YU, H. Y.,WU, I. H.,CHEN, Y. S.,HUANG, S. C.,KO, W. J. & WANG, S. S. 2014. Heart transplantation in endstage rheumatic heart disease-experience of an endemic area. *Circ J*, 78, 1900-7.
- CLLIERS, A. M. 2014. *Rheumatic fever and rheumatic heart disease in Gauteng on the decline: Experience at Chris Hani Baragwanath Academic Hospital, Johannesburg, South Africa*.
- CITY OF JOHANNESBURG METROPOLITAN MUNICIPALITY. 2011. *The remaking of Soweto 2006-2011* [Online]. Johannesburg: Central Strategy Unit  
Office of the Executive Mayor  
City of Johannesburg. [Accessed 23/09/2014 2014].
- CLUR, S. A. 2006. Frequency and severity of rheumatic heart disease in the catchment area of Gauteng hospitals, 1993-1995. *Samj South African Medical Journal*, 96, 233-237.
- COHEN, M.,POCOCK, W. A.,LAKIER, J. B.,MCLAREN, M. J.,LACHMAN, A. S. & BARLOW, J. B. 1978. Four year follow-up of black schoolchildren with non-ejection systolic clicks and mitral systolic murmurs. *Am Heart J*, 95, 697-701.
- COLQUHOUN, S. M.,CARAPETIS, J. R.,KADO, J. H. & STEER, A. C. 2009. Rheumatic heart disease and its control in the Pacific. *Expert Rev Cardiovasc Ther*, 7, 1517-24.
- COLQUHOUN, S. M.,CARAPETIS, J. R.,KADO, J. H.,REEVES, B. M.,REMENYI, B.,MAY, W.,WILSON, N. J. & STEER, A. C. 2013. Pilot study of nurse-led rheumatic heart disease echocardiography screening in Fiji--a novel approach in a resource-poor setting. *Cardiol Young*, 23, 546-52.
- COLQUHOUN, S. M.,KADO, J. H.,REMENYI, B.,WILSON, N. J.,CARAPETIS, J. R. & STEER, A. C. 2014. Echocardiographic screening in a resource poor setting: borderline rheumatic heart disease could be a normal variant. *Int J Cardiol*, 173, 284-9.
- CRAMP, G.,STONEHOUSE, M.,WEBB, R.,WEBB, R.,CHAFFEY-AUPOURI, G. & WILSON, N. 2012. Undetected rheumatic heart disease revealed using portable echocardiography in a population of school students in Tairāwhiti, New Zealand. *N Z Med J*, 125, 53-64.
- DAMASCENO, A.,MAYOSI, B. M.,SANI, M.,OGAH, O. S.,MONDO, C.,OJJI, D.,DZUDIE, A.,KOUAM, C. K.,SULIMAN, A.,SCHRUEDER, N.,YONGA, G.,BA, S. A.,MARU, F.,ALEMAYEHU, B.,EDWARDS, C.,DAVISON, B. A.,COTTER, G. & SLIWA, K. 2012. The causes, treatment, and outcome of acute heart failure in 1006 Africans from 9 countries. *Arch Intern Med*, 172, 1386-94.
- DE CATERINA, R.,HUSTED, S.,WALLENTIN, L.,ANDREOTTI, F.,ARNESEN, H.,BACHMANN, F.,BAIGENT, C.,HUBER, K.,JESPERSEN, J.,KRISTENSEN, S. D.,LIP, G. Y.,MORAIS, J.,RASMUSSEN, L. H.,SIEGBAHN, A.,VERHEUGT, F. W. & WEITZ, J. I. 2013. Vitamin K antagonists in heart disease: current status and perspectives (Section III). Position paper of the ESC Working Group on Thrombosis--Task Force on Anticoagulants in Heart Disease. *Thromb Haemost*, 110, 1087-107.
- DEARANI, J. A.,NEIROTTI, R.,KOHNEKE, E. J.,SINHA, K. K.,CABALKA, A. K.,BARNES, R. D.,JACOBS, J. P.,STELLIN, G.,TCHERVENKOV, C. I. & CUSHING, J. C. 2010. Improving pediatric cardiac surgical care in developing countries: matching resources to needs. *Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu*, 13, 35-43.
- DEGROFF, C. G. 2010. Letter by DeGroff regarding article, "Rheumatic heart disease screening by echocardiography: The inadequacy of World Health Organization criteria for optimizing the diagnosis of subclinical disease". *Circulation*, 121, e421; author reply e423.
- DEMIRBAG, R.,SADE, L. E.,AYDIN, M.,BOZKURT, A. & ACARTURK, E. 2013. The Turkish registry of heart valve disease. *Turk Kardiyol Dern Ars*, 41, 1-10.
- DEPARTMENT OF HEALTH- DIRECTOR GENERAL OF HEALTH. 2003. *South African Demographic and Health Survey (SADHS)* [Online]. Available: <http://www.info.gov.za/view/DownloadFileAction?id=90143> [Accessed 12 January 2014].
- DEPARTMENT OF HEALTH, S. A. 2003. *National Guidelines on the Primary Prevention and Prophylaxis of Rheumatic Fever and Rheumatic Heart Disease for Health Professionals at Primary Level*. [Online]. Pretoria: DOH, 1977. <http://www.doh.gov.za/docs/facts-f.html> (Last accessed 12/11/2013).

- DIAO, M., KANE, A., NDIAYE, M. B., MBAYE, A., BODIAN, M., DIA, M. M., SARR, M., KANE, A., MONSUEZ, J.-J. & BA, S. A. 2011. Pregnancy in women with heart disease in sub-Saharan Africa. *Archives of Cardiovascular Diseases*, 104, 370-374.
- DOLARA, A. 2008. The decline of cardiac auscultation: 'the ball of the match point is poised on the net'. *J Cardiovasc Med (Hagerstown)*, 9, 1173-4.
- ELLIS, D. J., USMAN, M. H., MILNER, P. G., CANAFAX, D. M. & EZEKOWITZ, M. D. 2009. The First Evaluation of a Novel Vitamin K Antagonist, Tecarfarin (ATI-5923), in Patients With Atrial Fibrillation. *Circulation*, 120, 1029-1035.
- ENGEL, M., ZÜHLKE, L. & ROBERTSON, K. A. 2009a. ASAP programme: Rheumatic fever and rheumatic heart disease: Where are we now in South Africa? *SA Heart* 6, 270-273.
- ENGEL, M. E., ZÜHLKE, L. J. & ROBERTSON, K. A. 2009b. ASAP programme: Rheumatic fever and rheumatic heart disease: Where are we now in South Africa? *SA Heart* 6, :270-273.
- ENGEL, M. E. 2012. *A Study of Determinants and Prevalence of Rheumatic Heart Disease in Cape Town*. PhD, University of Cape Town.
- ENGEL, M. E., HAILEAMLAK, A., ZÜHLKE, L., LEMMER, C. E., NKEPU, S., WALL, M. V. D., DANIEL, W., KING, M. S. & MAYOSI, B. M. 2015. Latent rheumatic heart disease in 4720 asymptomatic schoolchildren from South Africa and Ethiopia. submitted.
- ENGEL, M. E., STANDER, R., VOGEL, J., ADEYEMO, A. A., MAYOSI, B. M. 2007. Genetic contribution to rheumatic fever: a systematic review and meta-analysis of twin studies. [Presented at the 8th National Congress of the South African Heart Association, Sun City, 22-25 November 2007]. *S Afr Med J* 97, 1094.
- ESSOP, M. R. & NKOMO, V. T. 2005. Rheumatic and nonrheumatic valvular heart disease: epidemiology, management, and prevention in Africa. *Circulation*, 112, 3584-91.
- FIGUEROA, F. E., FERNANDEZ, M. S., VALDES, P., WILSON, C., LANAS, F., CARRION, F., BERRIOS, X. & VALDES, F. 2001. Prospective comparison of clinical and echocardiographic diagnosis of rheumatic carditis: long term follow up of patients with subclinical disease. *Heart*, 85, 407-10.
- FOURIE, P. 2009. Development of a hand-held device for automated Paediatric cardiac auscultation. *S A Heart*, 6, 263.
- GELDENHUYS, A. 2011. *Tenyear propensity matched cohort analysis of mitral valve repair and replacement for rheumatic heart disease at Groote Schuur Hospital*. M Med, University of Cape Town.
- GELDENHUYS, A., KOSHY, J. J., HUMAN, P. A., MTWALE, J. F., BRINK, J. G. & ZILLA, P. 2012. Rheumatic mitral repair versus replacement in a threshold country: the impact of commissural fusion. *J Heart Valve Dis*, 21, 424-32.
- GLAS, A. S., LIJMER, J. G., PRINS, M. H., BONSEL, G. J. & BOSSUYT, P. M. M. 2003. The diagnostic odds ratio: a single indicator of test performance. *Journal of Clinical Epidemiology*, 56, 1129-1135.
- GODOWN, J., LU, J. C., BEATON, A., SABLE, C., MIREMBE, G., SANYA, R., ALIKU, T., YU, S., LWABI, P., WEBB, C. L. & ENSING, G. J. 2015. Handheld echocardiography versus auscultation for detection of rheumatic heart disease. *Pediatrics*, 135, e939-44.
- GRIMALDI, A., AMMIRATI, E., MIRABEL, M. & MARIJON, E. 2012. Challenges of using ultrasounds for subclinical rheumatic heart disease screening. *Int J Cardiol*, pii: S0167-5273(12)01566-5.
- GUILHERME, L., CURY, P., DEMARCHI, L. M., COELHO, V., ABEL, L., LOPEZ, A. P., OSHIRO, S. E., ALIOTTI, S., CUNHA-NETO, E., POMERANTZEFF, P. M., TANAKA, A. C. & KALIL, J. 2004. Rheumatic heart disease: proinflammatory cytokines play a role in the progression and maintenance of valvular lesions. *Am J Pathol*, 165, 1583-91.
- GUILHERME, L., POSTOL, E., FRESCHI DE BARROS, S., HIGA, F., ALENCAR, R., LASTRE, M., ZAYAS, C., PUSCHEL, C. R., SILVA, W. R., SA-ROCHA, L. C., SA-ROCHA, V. M., PEREZ, O. & KALIL, J. 2009. A vaccine against *S. pyogenes*: design and experimental immune response. *Methods*, 49, 316-21.
- GUILHERME, L., KOHLER, K. F. & KALIL, J. 2011. Rheumatic heart disease: mediation by complex immune events. *Adv Clin Chem*, 53, 31-50.
- GULL, W. W. & SUTTON, H. G. 1869. Remarks on the Natural History of Rheumatic Fever. *Med Chir Trans*, 52, 43-84.

- GUNTHER, G., ASMERA, J. & PARRY, E. 2006. Death from rheumatic heart disease in rural Ethiopia. *Lancet*, 367, 391.
- HAMMERMEISTER, K. E., BURCHFIEL, C., JOHNSON, R. & GROVER, F. L. 1990. Identification of patients at greatest risk for developing major complications at cardiac surgery. *Circulation*, 82, Iv380-9.
- HANNA, I. R. & SILVERMAN, M. E. 2002. A history of cardiac auscultation and some of its contributors. *Am J Cardiol*, 90, 259-67.
- HEALEY, J. S., OLDGREN, J., PAREKH, A., COMMERFORD, P. J., AVEZUM, A., PAIS, P., ZHU, J., JANSKY, P., SIGAMI, A., MORILLO, C. A., LIU, L., DAMASCENO, A., GRINVALDS, A., REILLY, P., EZEKOWITZ, M., WALLENTIN, L., CONNOLLY, S. J. & YUSUF, S. 2011. Global variation in the etiology and management of atrial fibrillation: Results from a global atrial fibrillation registry. *Circulation*, 124.
- HEWITSON, J., BRINK, J. & ZILLA, P. 2002. The challenge of pediatric cardiac services in the developing world. *Semin Thorac Cardiovasc Surg*, 14, 340-5.
- HEWITSON, J. & ZILLA, P. 2010. Children's heart disease in sub-Saharan Africa: Challenging the burden of disease. *S A Heart*, 7, 18-29.
- HIGGINS, J. P. & THOMPSON, S. G. 2002. Quantifying heterogeneity in a meta-analysis. *Stat Med*, 21, 1539-58.
- HOOPEN, E. G., CILLIERS, A. M., HUGO-HAMMAN, C. T., BROWN, S. C., LAWRENSON, J. B., ZUHLKE, L. & HEWITSON, J. 2011. Paediatric cardiac services in South Africa. *S Afr Med J*, 101, 106-7.
- JACKSON, S. J., STEER, A. C. & CAMPBELL, H. 2011. Systematic Review: Estimation of global burden of non-suppurative sequelae of upper respiratory tract infection: rheumatic fever and post-streptococcal glomerulonephritis. *Trop Med Int Health*, 16, 2-11.
- JAFFE, W. M., ROCHE, A. H., COVERDALE, H. A., MCALISTER, H. F., ORMISTON, J. A. & GREENE, E. R. 1988. Clinical evaluation versus Doppler echocardiography in the quantitative assessment of valvular heart disease. *Circulation*, 78, 267-75.
- KANE, A., MIRABEL, M., TOURE, K., PERIER, M. C., FAZAA, S., TAFFLET, M., KARAM, N., ZOURAK, I., DIAGNE, D., MBAYE, A., KANE, M., DIACK, B., JOUVEN, X. & MARIJON, E. 2012. Echocardiographic screening for rheumatic heart disease: Age matters. *Int J Cardiol*, pii: S0167-5273(12)01608-7.
- KARAASLAN, S., DEMIROREN, S., ORAN, B., BAYSAL, T., BASPINAR, O. & UCAR, C. 2003. Criteria for judging the improvement in subclinical rheumatic valvitis. *Cardiol Young*, 13, 500-5.
- KARTHIKEYAN, G. & MAYOSI, B. M. 2009. Is primary prevention of rheumatic fever the missing link in the control of rheumatic heart disease in Africa? *Circulation*, 120, 709-13.
- KARTHIKEYAN, G., ZUHLKE, L., ENGEL, M., RANGARAJAN, S., YUSUF, S., TEO, K. & MAYOSI, B. M. 2012a. Rationale and design of a Global Rheumatic Heart Disease Registry: the REMEDY study. *Am Heart J*, 163, 535-40 e1.
- KARTHIKEYAN, G., ZUHLKE, L., ENGEL, M., RANGARAJAN, S., YUSUF, S., TEO, K. & MAYOSI, B. M. 2012b. Rationale and design of a Global Rheumatic Heart Disease Registry: The REMEDY study. *American Heart Journal*, 163, 535-+.
- KOEGELENBERG, C. F., DOUBELL, A. F., ORTH, H. & REUTER, H. 2003. Infective endocarditis in the Western Cape Province of South Africa: a three-year prospective study. *QJM*, 96, 217-25.
- KOLO, P. M., SANYA, E. O., OMOTOSHO, A. B., CHIJOKE, A. & DADA, S. A. 2010. The role of echocardiography in the management of stroke. *West Afr J Med*, 29, 239-43.
- KOTHARI, S. S. 2010. Letter by Kothari regarding article, "Rheumatic heart disease screening by echocardiography: The inadequacy of World Health Organization criteria for optimizing the diagnosis of subclinical disease". *Circulation*, 121, e420; author reply e423.
- LANNA, C. C., TONELLI, E., BARROS, M. V., GOULART, E. M. & MOTA, C. C. 2003. Subclinical rheumatic valvitis: a long-term follow-up. *Cardiol Young*, 13, 431-8.
- LANZA, R. P., COOPER, D. K. C. & BOYD, S. T. 1984. Comparison of patients with ischemic, myopathic, and rheumatic heart diseases as cardiac transplant recipients. *American Heart Journal*, 107, 8-12.

- LAWRENCE, J. G., CARAPETIS, J. R., GRIFFITHS, K., EDWARDS, K. & CONDON, J. R. 2013. Acute rheumatic fever and rheumatic heart disease: incidence and progression in the Northern Territory of Australia, 1997 to 2010. *Circulation*, 128, 492-501.
- LEIBBRANDT, M., WOOLARD, I., FINN, A. & ARGENT, J. 2010. Trends in South African Income Distribution and Poverty since the Fall of Apartheid. *OECD Social, Employment and Migration Working Papers*, No 101.
- LIM, S. S., VOS, T., FLAXMAN, A. D., DANAEI, G., SHIBUYA, K., ADAIR-ROHANI, H., AMANN, M., ANDERSON, H. R., ANDREWS, K. G., ARYEE, M., ATKINSON, C., BACCHUS, L. J., BAHALIM, A. N., BALAKRISHNAN, K., BALMES, J., BARKER-COLLO, S., BAXTER, A., BELL, M. L., BLORE, J. D., BLYTH, F., BONNER, C., BORGES, G., BOURNE, R., BOUSSINESQ, M., BRAUER, M., BROOKS, P., BRUCE, N. G., BRUNEKREEF, B., BRYAN-HANCOCK, C., BUCELLO, C., BUCHBINDER, R., BULL, F., BURNETT, R. T., BYERS, T. E., CALABRIA, B., CARAPETIS, J., CARNAHAN, E., CHAFE, Z., CHARLSON, F., CHEN, H., CHEN, J. S., CHENG, A. T., CHILD, J. C., COHEN, A., COLSON, K. E., COWIE, B. C., DARBY, S., DARLING, S., DAVIS, A., DEGENHARDT, L., DENTENER, F., DES JARLAIS, D. C., DEVRIES, K., DHERANI, M., DING, E. L., DORSEY, E. R., DRISCOLL, T., EDMOND, K., ALI, S. E., ENGELL, R. E., ERWIN, P. J., FAHIMI, S., FALDER, G., FARZADFAR, F., FERRARI, A., FINUCANE, M. M., FLAXMAN, S., FOWKES, F. G., FREEDMAN, G., FREEMAN, M. K., GAKIDOU, E., GHOSH, S., GIOVANNUCCI, E., GMEL, G., GRAHAM, K., GRAINGER, R., GRANT, B., GUNNELL, D., GUTIERREZ, H. R., HALL, W., HOEK, H. W., HOGAN, A., HOSGOOD, H. D., 3RD, HOY, D., HU, H., HUBBELL, B. J., HUTCHINGS, S. J., IBEANUSI, S. E., JACKLYN, G. L., JASRASARIA, R., JONAS, J. B., KAN, H., KANIS, J. A., KASSEBAUM, N., KAWAKAMI, N., KHANG, Y. H., KHATIBZADEH, S., KHOO, J. P., KOK, C., LADEN, F., et al. 2012. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet*, 380, 2224-60.
- LONGO-MBENZA, B., BAYEKULA, M., NGIYULU, R., KINTOKI, V. E., BIKANGI, N. F., SEGHERS, K. V., LUKOKI, L. E., MANDUNDU, M. F., MANZANZA, M. & NLANDU, Y. 1998. Survey of rheumatic heart disease in school children of Kinshasa town. *Int J Cardiol*, 63, 287-94.
- LOZANO, R., NAGHAVI, M., FOREMAN, K., LIM, S., SHIBUYA, K., ABOYANS, V., ABRAHAM, J., ADAIR, T., AGGARWAL, R., AHN, S. Y., ALVARADO, M., ANDERSON, H. R., ANDERSON, L. M., ANDREWS, K. G., ATKINSON, C., BADDOUR, L. M., BARKER-COLLO, S., BARTELS, D. H., BELL, M. L., BENJAMIN, E. J., BENNETT, D., BHALLA, K., BIKBOV, B., BIN ABDULHAK, A., BIRBECK, G., BLYTH, F., BOLLIGER, I., BOUFIOUS, S., BUCELLO, C., BURCH, M., BURNEY, P., CARAPETIS, J., CHEN, H., CHOU, D., CHUGH, S. S., COFFENG, L. E., COLAN, S. D., COLQUHOUN, S., COLSON, K. E., CONDON, J., CONNOR, M. D., COOPER, L. T., CORRIERE, M., CORTINOVIS, M., DE VACCARO, K. C., COUSER, W., COWIE, B. C., CRIQUI, M. H., CROSS, M., DABHADKAR, K. C., DAHODWALA, N., DE LEO, D., DEGENHARDT, L., DELOSSANTOS, A., DENENBERG, J., DES JARLAIS, D. C., DHARMARATNE, S. D., DORSEY, E. R., DRISCOLL, T., DUBER, H., EBEL, B., ERWIN, P. J., ESPINDOLA, P., EZZATI, M., FEIGIN, V., FLAXMAN, A. D., FOROUZANFAR, M. H., FOWKES, F. G., FRANKLIN, R., FRANSEN, M., FREEMAN, M. K., GABRIEL, S. E., GAKIDOU, E., GASPARI, F., GILLUM, R. F., GONZALEZ-MEDINA, D., HALASA, Y. A., HARING, D., HARRISON, J. E., HAVMOELLER, R., HAY, R. J., HOEN, B., HOTEZ, P. J., HOY, D., JACOBSEN, K. H., JAMES, S. L., JASRASARIA, R., JAYARAMAN, S., JOHNS, N., KARTHIKEYAN, G., KASSEBAUM, N., KEREN, A., KHOO, J. P., KNOWLTON, L. M., KOBUSINGYE, O., KORANTENG, A., KRISHNAMURTHI, R., LIPNICK, M., LIPSHULTZ, S. E., OHNO, S. L., et al. 2012. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet*, 380, 2095-128.
- LU, J. C., SABLE, C., ENSING, G. J., WEBB, C., SCHEEL, J., ALIKU, T., LWABI, P., GODOWN, J. & BEATON, A. 2015. Simplified rheumatic heart disease screening criteria for handheld echocardiography. *J Am Soc Echocardiogr*, 28, 463-9.
- LUE, H. C., CHEN, C. L. & WEI, H. 1976. Some problems in long-term prevention of streptococcal infection among children with rheumatic heart disease in Taiwan. *Jpn Heart J*, 17, 550-9.
- MAHARAJ, B., DYER, R. B., LEARY, W. P., ARBUCKLE, D. D., ARMSTRONG, T. G. & PUDIFIN, D. J. 1987. Screening for rheumatic heart disease amongst black schoolchildren in Inanda, South Africa. *J Trop Pediatr*, 33, 60-1.



- MANYEMBA, J. & MAYOSI, B. M. 2003. Intramuscular penicillin is more effective than oral penicillin in secondary prevention of rheumatic fever--a systematic review. *S Afr Med J*, 93, 212-218.
- MARCUS, R. H., SARELI, P., POCOCK, W. A. & BARLOW, J. B. 1994. The spectrum of severe rheumatic mitral valve disease in a developing country. Correlations among clinical presentation, surgical pathologic findings, and hemodynamic sequelae. *Ann Intern Med*, 120, 177-83.
- MARIJON, E., TIVANE, A., VOICU, S., VILANCULOS, A., JANI, D., FERREIRA, B. & OU, P. 2006. Prevalence of congenital heart disease in schoolchildren of sub-Saharan Africa, Mozambique. *Int J Cardiol*, 113, 440-1.
- MARIJON, E., OU, P., CELERMAJER, D. S., FERREIRA, B., MOCUMBI, A. O., JANI, D., PAQUET, C., JACOB, S., SIDI, D. & JOUVEN, X. 2007. Prevalence of rheumatic heart disease detected by echocardiographic screening. *N Engl J Med*, 357, 470-6.
- MARIJON, E., TAFFLET, M. & JOUVEN, X. 2008. Time to use ultrasound and not stethoscopes for rheumatic heart disease screening. *Nat Clin Pract Cardiovasc Med*, 5, E1-3.
- MARIJON, E., CELERMAJER, D. S., TAFFLET, M., EL-HAOU, S., JANI, D. N., FERREIRA, B., MOCUMBI, A. O., PAQUET, C., SIDI, D. & JOUVEN, X. 2009. Rheumatic heart disease screening by echocardiography: the inadequacy of World Health Organization criteria for optimizing the diagnosis of subclinical disease. *Circulation*, 120, 663-8.
- MARIJON, E., MIRABEL, M., CELERMAJER, D. S. & JOUVEN, X. 2012. Rheumatic heart disease. *The Lancet*, 379, 953-964.
- MAYOSI, B., ROBERTSON, K., VOLMINK, J., ADEBO, W., AKINYORE, K., AMOAH, A., BANNERMAN, C., BIESMAN-SIMONS, S., CARAPETIS, J., CILLIERS, A., COMMERFORD, P., CROASDALE, A., DAMASCENO, A., DEAN, J., DEAN, M., DE SOUZA, R., FILIPE, A., HUGO-HAMMAN, C., JURGENS-CLUR, S. A., KOMBILA-KOUMBA, P., KOTZENBERG, C., LAWRENSON, J., MANGA, P., MATENGA, J., MATHIVHA, T., MNTLA, P., MOCUMBI, A., MOKONE, T., OGOLA, E., OMOKHODION, S., PALWENI, C., PEARCE, A., SALO, A., THOMAS, B., WALKER, K., WIYSONGE, C. & ZAHER, S. 2006. The Drakensberg declaration on the control of rheumatic fever and rheumatic heart disease in Africa. *S Afr Med J*, 96, 246.
- MAYOSI, B. 2009. The four pillars of rheumatic heart disease control. *S Afr Med J*, 100, 506.
- MAYOSI, B. M. 2007. Contemporary trends in the epidemiology and management of cardiomyopathy and pericarditis in sub-Saharan Africa. *Heart*, 93, 1176-83.
- MAYOSI, B. M. 2012. Letter regarding article, "Echocardiography screening for rheumatic heart disease in Ugandan schoolchildren". *Circulation*, 126, e476; author reply e478-9.
- MAYOSI, B. M., LAWN, J. E., VAN NIEKERK, A., BRADSHAW, D., ABDOL KARIM, S. S. & COOVADIA, H. M. 2012. Health in South Africa: changes and challenges since 2009. *Lancet*, 380, 2029-43.
- MAYOSI, B. M. 2014. The challenge of silent rheumatic heart disease. *Lancet Glob Health*, 2, e677-8.
- MAYOSI, B. M. & BENATAR, S. R. 2014. Health and health care in South Africa--20 years after Mandela. *N Engl J Med*, 371, 1344-53.
- MAYOSI, B. M., GAMRA, H., DANGOU, J. M. & KASONDE, J. 2014. Rheumatic heart disease in Africa: the Mosi-o-Tunya call to action. *Lancet Glob Health*, 2, e438-9.
- MCDONALD, M., BROWN, A., NOONAN, S. & CARAPETIS, J. R. 2005. Preventing recurrent rheumatic fever: the role of register based programmes. *Heart*, 91, 1131-3.
- MCDONALD, M., TOWERS, R., FAGAN, P., MCKINNON, M., BENDER, N., ANDREWS, R., CURRIE, B. J. & CARAPETIS, J. 2006. Recovering streptococci from the throat, a practical alternative to direct plating in remote tropical communities. *J Clin Microbiol*, 44, 547-52.
- MCLAREN, M. J., HAWKINS, D. M., KOORNHOF, H. J., BLOOM, K. R., BRAMWELL-JONES, D. M., COHEN, E., GALE, G. E., KANAREK, K., LACHMAN, A. S., LAKIER, J. B., POCOCK, W. A. & BARLOW, J. B. 1975. Epidemiology of rheumatic heart disease in black schoolchildren of Soweto, Johannesburg. *Br Med J*, 3, 474-8.
- MCLAREN, M. J., MARKOWITZ, M. & GERBER, M. A. 1994. Rheumatic heart disease in developing countries: the consequence of inadequate prevention. *Ann Intern Med*, 120, 243-5.
- MILANOVIC, B. 2012. "Global Inequality: From Class to Location, from Proletarians to Migrants,". *Global Policy, London School of Economics and Political Science*, 3, 125-134.

- MILNE, R. J., LENNON, D. R., STEWART, J. M., VANDER HOORN, S. & SCUFFHAM, P. A. 2012a. Incidence of acute rheumatic fever in New Zealand children and youth. *J Paediatr Child Health*, 48, 685-91.
- MILNE, R. J., LENNON, D. R., STEWART, J. M., VANDER HOORN, S. & SCUFFHAM, P. A. 2012b. Incidence of acute rheumatic fever in New Zealand children and youth. *Journal of Paediatrics and Child Health*, 48, 685-691.
- MINICH, L. L., TANI, L. Y., PAGOTTO, L. T., SHADDY, R. E. & VEASY, L. G. 1997. Doppler echocardiography distinguishes between physiologic and pathologic "silent" mitral regurgitation in patients with rheumatic fever. *Clin Cardiol*, 20, 924-6.
- MIRABEL, M., CELERMAJER, D. S., FERREIRA, B., TAFFLET, M., PERIER, M. C., KARAM, N., MOCUMBI, A. O., JANI, D. N., SIDI, D., JOUVEN, X. & MARIJON, E. 2012a. Screening for rheumatic heart disease: evaluation of a simplified echocardiography-based approach. *Eur Heart J Cardiovasc Imaging*.
- MIRABEL, M., CELERMAJER, D. S., FERREIRA, B., TAFFLET, M., PERIER, M. C., KARAM, N., MOCUMBI, A. O., JANI, D. N., SIDI, D., JOUVEN, X. & MARIJON, E. 2012b. Screening for rheumatic heart disease: evaluation of a simplified echocardiography-based approach. *Eur Heart J Cardiovasc Imaging*, 13, 1024-9.
- MIRABEL, M., BACQUELIN, R., TAFFLET, M., ROBILLARD, C., HUON, B., CORSENAC, P., DE FREMICOURT, I., NARAYANAN, K., MEUNIER, J. M., NOEL, B., HAGEGE, A. A., ROUCHON, B., JOUVEN, X. & MARIJON, E. 2015. Screening for rheumatic heart disease: evaluation of a focused cardiac ultrasound approach. *Circ Cardiovasc Imaging*, 8.
- MOCUMBI, A. O. 2012. The challenges of cardiac surgery for African children. *Cardiovascular Journal of Africa*, 23, 165-167.
- MOCUMBI, A. O. & SLIWA, K. 2012. Women's cardiovascular health in Africa. *Heart*, 98, 450-455.
- MOHER, D., LIBERATI, A., TETZLAFF, J. & ALTMAN, D. G. 2009. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Journal of Clinical Epidemiology*, 62, 1006-12.
- MURRAY, C. J., EZZATI, M., FLAXMAN, A. D., LIM, S., LOZANO, R., MICHAUD, C., NAGHAVI, M., SALOMON, J. A., SHIBUYA, K., VOS, T., WIKLER, D. & LOPEZ, A. D. 2012a. GBD 2010: design, definitions, and metrics. *Lancet*, 380, 2063-6.
- MURRAY, C. J. L., VOS, T., LOZANO, R., NAGHAVI, M., FLAXMAN, A. D., MICHAUD, C., EZZATI, M., SHIBUYA, K., SALOMON, J. A., ABDALLA, S., ABOYANS, V., ABRAHAM, J., ACKERMAN, I., AGGARWAL, R., AHN, S. Y., ALI, M. K., ALVARADO, M., ANDERSON, H. R., ANDERSON, L. M., ANDREWS, K. G., ATKINSON, C., BADDOUR, L. M., BAHALIM, A. N., BARKER-COLLO, S., BARRERO, L. H., BARTELS, D. H., BASÁÑEZ, M.-G., BAXTER, A., BELL, M. L., BENJAMIN, E. J., BENNETT, D., BERNABÉ, E., BHALLA, K., BHANDARI, B., BIKBOV, B., ABDULHAK, A. B., BIRBECK, G., BLACK, J. A., BLENCOWE, H., BLORE, J. D., BLYTH, F., BOLLIGER, I., BONAVENTURE, A., BOUFIOUS, S., BOURNE, R., BOUSSINESQ, M., BRAITHWAITE, T., BRAYNE, C., BRIDGETT, L., BROOKER, S., BROOKS, P., BRUGHA, T. S., BRYAN-HANCOCK, C., BUCELLO, C., BUCHBINDER, R., BUCKLE, G., BUDKE, C. M., BURCH, M., BURNEY, P., BURSTEIN, R., CALABRIA, B., CAMPBELL, B., CANTER, C. E., CARABIN, H., CARAPETIS, J., CARMONA, L., CELLA, C., CHARLSON, F., CHEN, H., CHENG, A. T.-A., CHOU, D., CHUGH, S. S., COFFENG, L. E., COLAN, S. D., COLQUHOUN, S., COLSON, K. E., CONDON, J., CONNOR, M. D., COOPER, L. T., CORRIERE, M., CORTINOVIS, M., DE VACCARO, K. C., COUSER, W., COWIE, B. C., CRIQUI, M. H., CROSS, M., DABHADKAR, K. C., DAHIYA, M., DAHODWALA, N., DAMSERE-DERRY, J., DANAEI, G., DAVIS, A., LEO, D. D., DEGENHARDT, L., DELLAVALLE, R., DELOSSANTOS, A., DENENBERG, J., DERRETT, S., DES JARLAIS, D. C., DHARMARATNE, S. D., et al. 2012b. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *The Lancet*, 380, 2197-2223.
- NISHIMURA, R. A., CARABELLO, B. A., FAXON, D. P., FREED, M. D., LYTLE, B. W., O'GARA, P. T., O'ROURKE, R. A., SHAH, P. M., BONOW, R. O., CHATTERJEE, K., DE LEON, A. C., JR., GAASCH, W. H., OTTO, C. M., SHANEWISE, J. S., SMITH, S. C., JR., JACOBS, A. K., BULLER, C. E., CREAGER, M. A., ETTINGER, S. M., KRUMHOLZ, H. M., KUSHNER, F. G., PAGE, R. L., TARKINGTON, L. G. & YANCY, C. W., JR. 2008. ACC/AHA 2008 guideline update on valvular heart disease: focused update on infective

- endocarditis: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines: endorsed by the Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *Circulation*, 118, 887-96.
- NISHIMURA, R. A., OTTO, C. M., BONOW, R. O., CARABELLO, B. A., ERWIN, J. P., 3RD, GUYTON, R. A., O'GARA, P. T., RUIZ, C. E., SKUBAS, N. J., SORAJJA, P., SUNDT, T. M., 3RD & THOMAS, J. D. 2014. 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*.
- NKGUDI, B., MAYOSI, B. M., ROBERTSON, K. A. & VOLMINK, J. 2006. Notification of rheumatic fever in South Africa - Evidence for underreporting by health care professionals and administrators. *South African Medical Journal*, 96, 206-208.
- NOPONEN, A. L., LUKKARINEN, S., ANGERLA, A. & SEPPONEN, R. 2007. Phono-spectrographic analysis of heart murmur in children. *BMC Pediatr*, 7, 23.
- NORDET, P., LOPEZ, R., DUENAS, A. & SARMIENTO, L. 2008. Prevention and control of rheumatic fever and rheumatic heart disease: the Cuban experience (1986-1996-2002). *Cardiovasc J Afr*, 19, 135-140.
- NTUSI, N. B. & MAYOSI, B. M. 2009. Epidemiology of heart failure in sub-Saharan Africa. *Expert Rev Cardiovasc Ther*, 7, 169-80.
- OGUNROMBI, A. B. 2011. *Sixteen year retrospective analysis of rheumatic and nonrheumatic heart disease patients undergoing valve procedures at Groote Schuur Hospital*. M Sc( Med), University of Cape Town.
- OKELLO, E., WANZHU, Z., MUSOKE, C., TWALIB, A., KAKANDE, B., LWABI, P., WILSON, N. B., MONDO, C. K., ODOI-ADOME, R. & FREERS, J. 2013. Cardiovascular complications in newly diagnosed rheumatic heart disease patients at Mulago Hospital, Uganda. *Cardiovasc J Afr*, 24, 80-5.
- OKUYAMA, Y., MATSUO, M., MATSUO, H., SAKAGUCHI, Y., TAKAI, H., HORIGUCHI, Y., RYOMOTO, T., ADACHI, S., AMANO, T., TOGAWA, M., MASUDA, M., MINAMIGUCHI, H., NANTO, S., KOMURO, I. & SAKATA, Y. 2014. Introduction of point-of-care testing in Japanese outpatient clinics is associated with improvement in time in therapeutic range in anticoagulant-treated patients. *Circ J*, 78, 1342-8.
- OLDGREN, J., HEALEY, J. S., EZEKOWITZ, M., COMMERFORD, P., AVEZUM, A., PAIS, P., ZHU, J., JANSKY, P., SIGAMANI, A., MORILLO, C. A., LIU, L., DAMASCENO, A., GRINVALDS, A., NAKAMYA, J., REILLY, P. A., KELTAI, K., VAN GELDER, I. C., YUSUFALI, A. H., WATANABE, E., WALLENTIN, L., CONNOLLY, S. J., YUSUF, S. & INVESTIGATORS, R.-L. A. F. R. 2014. Variations in cause and management of atrial fibrillation in a prospective registry of 15,400 emergency department patients in 46 countries: the RE-LY Atrial Fibrillation Registry. *Circulation*, 129, 1568-76.
- OMOKHODION, S. I. & LAGUNJU, I. A. 2005. Prognostic indices in childhood heart failure. *West Afr J Med*, 24, 325-8.
- OZKUTLU, S., HALLIOGLU, O. & AYABAKAN, C. 2003. Evaluation of subclinical valvar disease in patients with rheumatic fever. *Cardiol Young*, 13, 495-9.
- PAAR, J. A., BERRIOS, N. M., ROSE, J. D., CACERES, M., PENNA, R., PEREZ, W., CHEN-MOK, M., JOLLES, E. & DALE, J. B. 2010. Prevalence of rheumatic heart disease in children and young adults in Nicaragua. *Am J Cardiol*, 105, 1809-14.
- PARKS, T., KADO, J., MILER, A., WARD, B., HEENAN, R., COLQUHOUN, S., TUKANA, I. & STEER, A. 2014. Mortality amongst patients with rheumatic heart disease in Fiji: a national historic data-linkage cohort study. *Global Heart*, Supplement: World Congress of Cardiology Scientific Sessions 2014: Vol 9, PM 471.
- PELAJO, C. F., LOPEZ-BENITEZ, J. M., TORRES, J. M. & DE OLIVEIRA, S. K. 2010. Adherence to secondary prophylaxis and disease recurrence in 536 Brazilian children with rheumatic fever. *Pediatr Rheumatol Online J*, 8, 22.
- POCOCK, W. A., CHESLER, E. & J.B., B. 1968. A preliminary survey of 428 Black Soweto schoolchildren aged 2-12 years. *Proceedings of the Southern Africa Cardiac Society Conference*.

- PRETORIUS, E., CRONJE, M. L. & STRYDOM, O. 2010. Development of a pediatric cardiac computer aided auscultation decision support system. *Conf Proc IEEE Eng Med Biol Soc*, 1, 6078-82.
- RALSTON, J. 2012. New global target on non-communicable diseases: a call to action for the global cardiovascular disease community. *Cardiovasc J Afr*, 23, 241-2.
- REEVES, B. M., KADO, J. & BROOK, M. 2011. High prevalence of rheumatic heart disease in Fiji detected by echocardiography screening. *J Paediatr Child Health*, 47, 473-8.
- REMENYI, B., WILSON, N., STEER, A., FERREIRA, B., KADO, J., KUMAR, K., LAWRENSON, J., MAGUIRE, G., MARIJON, E., MIRABEL, M., MOCUMBI, A. O., MOTA, C., PAAR, J., SAXENA, A., SCHEEL, J., STIRLING, J., VIALI, S., BALEKUNDRI, V. I., WHEATON, G., ZUHLKE, L. & CARAPETIS, J. 2012a. World Heart Federation criteria for echocardiographic diagnosis of rheumatic heart disease--an evidence-based guideline. *Nat Rev Cardiol*, 9, 297-309.
- REMENYI, B., WILSON, N., STEER, A., FERREIRA, B., KADO, J., KUMAR, K., LAWRENSON, J., MAGUIRE, G., MARIJON, E., MIRABEL, M., MOCUMBI, A. O., MOTA, C., PAAR, J., SAXENA, A., SCHEEL, J., STIRLING, J., VIALI, S., BALEKUNDRI, V. I., WHEATON, G., ZUHLKE, L. & CARAPETIS, J. 2012b. World Heart Federation criteria for echocardiographic diagnosis of rheumatic heart disease - an evidence-based guideline. *Nat Rev Cardiol*, 9, 297-309.
- REMENYI, B., CARAPETIS, J., WYBER, R., TAUBERT, K. & MAYOSI, B. M. 2013. Position statement of the World Heart Federation on the prevention and control of rheumatic heart disease. *Nat Rev Cardiol*, 10, 284-92.
- REMOND, M. G., SEVERIN, K. L., HODDER, Y., MARTIN, J., NELSON, C., ATKINSON, D. & MAGUIRE, G. P. 2013. Variability in disease burden and management of rheumatic fever and rheumatic heart disease in two regions of tropical Australia. *Intern Med J*, 43, 386-93.
- RHDAUSTRALIA (ARF/RHD WRITING GROUP) NATIONAL HEART FOUNDATION OF AUSTRALIA AND THE CARDIAC SOCIETY OF AUSTRALIA AND NEW ZEALAND. 2012. *The Australian guideline for prevention, diagnosis and management of acute rheumatic fever and rheumatic heart disease (2nd edition)* [Online]. Available: [http://www.rhdaustralia.org.au/sites/default/files/guideline\\_0.pdf](http://www.rhdaustralia.org.au/sites/default/files/guideline_0.pdf) [Accessed 12 October 2014].
- ROBERTS, K., COLQUHOUN, S., STEER, A., REMENYI, B. & CARAPETIS, J. 2013a. Screening for rheumatic heart disease: current approaches and controversies. *Nat Rev Cardiol*, 10, 49-58.
- ROBERTS, K., MAGUIRE, G., BROWN, A., ATKINSON, D., REMENYI, B., ILTON, M., WHEATON, G., KELLY, A., KUMAR, K. & CARAPETIS, J. 2013b. Prevalence of rheumatic Heart Disease in high-risk children in Northern Australia: application of the 2012 World Heart Federation criteria: abstract no 815. *SA Heart*, 10, 270.
- ROBERTS, K. V., BROWN, A. D., MAGUIRE, G. P., ATKINSON, D. N. & CARAPETIS, J. R. 2013c. Utility of auscultatory screening for detecting rheumatic heart disease in high-risk children in Australia's Northern Territory. *Med J Aust*, 199, 196-9.
- ROTHENBUHLER, M., O'SULLIVAN, C. J., STORTECKY, S., STEFANINI, G. G., SPITZER, E., ESTILL, J., SHRESTHA, N. R., KEISER, O., JUNI, P. & PILGRIM, T. 2014. Active surveillance for rheumatic heart disease in endemic regions: a systematic review and meta-analysis of prevalence among children and adolescents. *Lancet Glob Health*, 2, e717-26.
- ROTHENBÜHLER, M., O'SULLIVAN, C. J., STORTECKY, S., STEFANINI, G. G., SPITZER, E., ESTILL, J., SHRESTHA, N. R., KEISER, O., JÜNI, P. & PILGRIM, T. 2014. Active surveillance for rheumatic heart disease in endemic regions: a systematic review and meta-analysis of prevalence among children and adolescents. *The Lancet Global Health*, 2, e717-e726.
- RUFF, C. T., GIUGLIANO, R. P., BRAUNWALD, E., HOFFMAN, E. B., DEENADAYALU, N., EZEKOWITZ, M. D., CAMM, A. J., WEITZ, J. I., LEWIS, B. S., PARKHOMENKO, A., YAMASHITA, T. & ANTMAN, E. M. 2014. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. *The Lancet*, 383, 955-962.
- SADIQ, M., ISLAM, K., ABID, R., LATIF, F., REHMAN, A. U., WAHEED, A., AZHAR, M. & KHAN, J. S. 2009. Prevalence of rheumatic heart disease in school children of urban Lahore. *Heart*, 95, 353-7.
- SANI, M. U., KARAYE, K. M. & BORODO, M. M. 2007a. Prevalence and pattern of rheumatic heart disease in the Nigerian savannah: an echocardiographic study. *Cardiovasc J Afr*, 18, 295-9.

- SANI, M. U., KARAYE, K. M. & IBRAHIM, D. A. 2007b. Cardiac morbidity in subjects referred for echocardiographic assessment at a tertiary medical institution in the Nigerian savanna zone. *Afr J Med Med Sci*, 36, 141-7.
- SARGEANT, J. M., KELTON, D. F. & O'CONNOR, A. M. 2014. Study designs and systematic reviews of interventions: building evidence across study designs. *Zoonoses Public Health*, 61 Suppl 1, 10-7.
- SAXENA, A., KUMAR, R. K., GERA, R. P., RADHAKRISHNAN, S., MISHRA, S. & AHMED, Z. 2008. Consensus guidelines on pediatric acute rheumatic fever and rheumatic heart disease. *Indian Pediatr*, 45, 565-73.
- SAXENA, A., RAMAKRISHNAN, S., ROY, A., SETH, S., KRISHNAN, A., MISRA, P., KALAIVANI, M., BHARGAVA, B., FLATHER, M. D. & POOLE-WILSON, P. P. 2011. Prevalence and outcome of subclinical rheumatic heart disease in India: the RHEUMATIC (Rheumatic Heart Echo Utilisation and Monitoring Actuarial Trends in Indian Children) study. *Heart*, 97, 2018-22.
- SAXENA, A. 2013. Echocardiographic Diagnosis of Chronic Rheumatic Valvular Lesions. *Global Heart*, 8, 203-212.
- SAXENA, A., ZÜHLKE, L. & WILSON, N. 2013. Echocardiographic Screening for Rheumatic Heart Disease: Issues for the Cardiology Community. *Global Heart*, Vol. 8 September, 197-202.
- SECKELER, M. D., HOKE, T. R., GURKA, M. J. & BARTON, L. L. 2010. No demonstrable effect of benzathine penicillin on recurrence of rheumatic Fever in pacific island population. *Pediatr Cardiol*, 31, 849-52.
- SECKELER, M. D. & HOKE, T. R. 2011. The worldwide epidemiology of acute rheumatic fever and rheumatic heart disease. *Clin Epidemiol*, 3, 67-84.
- SKOULARIGIS, J. S., V. JOUBERT, GINA. SARELI PINHAS 1994. Evaluation of the long-term results of mitral valve repair in 254 young patients with theumatic mitral regurgitation. *Circulation*, 90(5), 167-174.
- SLIWA, K., CARRINGTON, M., MAYOSI, B. M., ZIGIRIADIS, E., MVUNGI, R. & STEWART, S. 2010. Incidence and characteristics of newly diagnosed rheumatic heart disease in urban African adults: insights from the heart of Soweto study. *Eur Heart J*, 31, 719-27.
- SMITH, S. C., JR., COLLINS, A., FERRARI, R., HOLMES, D. R., JR., LOGSTRUP, S., MCGHIE, D. V., RALSTON, J., SACCO, R. L., STAM, H., TAUBERT, K., WOOD, D. A. & ZOGHBI, W. A. 2012. Our time: a call to save preventable death from cardiovascular disease (heart disease and stroke). *Circulation*, 126, 2769-75.
- SOLIMAN, E. Z. & JUMA, H. 2008. Cardiac disease patterns in northern Malawi: epidemiologic transition perspective. *J Epidemiol*, 18, 204-8.
- STATISTICS SA'S MORTALITY AND CAUSES OF DEATH IN SOUTH AFRICA REPORT FOR 2011. 2014. *Decline in South Africa's mortality rate continues* [Online]. Available: <http://www.southafrica.info/about/health/mortality-190314.htm#.VF817fmUd8E>.
- STATISTICS SOUTH AFRICA 2005. Statistical release P0309.3. *Mortality and causes of death in South Africa: Findings from death notification*. Statistics South Africa.
- STATISTICS SOUTH AFRICA 2006. Statistical release P0309.3. *Mortality and causes of death in South Africa: Findings from death notification*. Statistics South Africa.
- STATISTICS SOUTH AFRICA 2007. Statistical release P0309.3. *Mortality and causes of death in South Africa: Findings from death notification*. Statistics South Africa.
- STATISTICS SOUTH AFRICA 2008. Statistical release P0309.3. *Mortality and causes of death in South Africa: Findings from death notification*. Statistics South Africa.
- STATISTICS SOUTH AFRICA 2009. Statistical release P0309.3. *Mortality and causes of death in South Africa: Findings from death notification*. Statistics South Africa.
- STATISTICS SOUTH AFRICA 2010. Statistical release P0309.3. *Mortality and causes of death in South Africa: Findings from death notification*. Statistics South Africa.
- STATISTICS SOUTH AFRICA 2011. Statistical release P0309.3. *Mortality and causes of death in South Africa: Findings from death notification*. Statistics South Africa.

- STATISTICS SOUTH AFRICA 2012. Statistical release P0309.3. *Mortality and causes of death in South Africa: Findings from death notification*. Statistics South Africa.
- STATISTICS SOUTH AFRICA 2013. Statistical release P0309.3. *Mortality and causes of death in South Africa: Findings from death notification*. Statistics South Africa.
- STATISTICS SOUTH AFRICA. 2014a. [http://beta2.statssa.gov.za/?page\\_id=1859](http://beta2.statssa.gov.za/?page_id=1859) [Online]. Statistics South Africa. Available: <http://beta2.statssa.gov.za/> [Accessed 24 September 2014 2014].
- STATISTICS SOUTH AFRICA 2014b. Statistical release P0309.3. *Mortality and causes of death in South Africa: Findings from death notification*. Statistics South Africa.
- STEER, A. C., CARAPETIS, J. R., NOLAN, T. M. & SHANN, F. 2002. Systematic review of rheumatic heart disease prevalence in children in developing countries: the role of environmental factors. *J Paediatr Child Health*, 38, 229-34.
- STEER, A. C. & CARAPETIS, J. R. 2009. Acute rheumatic fever and rheumatic heart disease in indigenous populations. *Pediatr Clin North Am*, 56, 1401-19.
- STEER, A. C., KADO, J., JENNEY, A. W., BATZLOFF, M., WAQATAKIREWA, L., MULHOLLAND, E. K. & CARAPETIS, J. R. 2009a. Acute rheumatic fever and rheumatic heart disease in Fiji: prospective surveillance, 2005-2007. *Med J Aust*, 190, 133-5.
- STEER, A. C., KADO, J., WILSON, N., TUIKETEI, T., BATZLOFF, M., WAQATAKIREWA, L., MULHOLLAND, E. K. & CARAPETIS, J. R. 2009b. High prevalence of rheumatic heart disease by clinical and echocardiographic screening among children in Fiji. *J Heart Valve Dis*, 18, 327-35; discussion 336.
- STEER, A. C., COLQUHOUN, S., KADO, J. & CARAPETIS, J. R. 2011. Secondary Prophylaxis is Important for the Prevention of Recurrent Rheumatic Fever in the Pacific. *Pediatr Cardiol*, 32, 864-5.
- STROUP, D. F., BERLIN, J. A., MORTON, S. C., OLKIN, I., WILLIAMSON, G. D., RENNIE, D., MOHER, D., BECKER, B. J., SIPE, T. A. & THACKER, S. B. 2000. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *Jama*, 283, 2008-12.
- SUCU, M., DAVUTOGLU, V., OZER, O. & AKSOY, M. 2010. Epidemiological, clinical and microbiological profile of infective endocarditis in a tertiary hospital in the South-East Anatolia Region. *Turk Kardiyol Dern Ars*, 38, 107-11.
- SUDEEP, D. D. & SREDHAR, K. 2013. The Descriptive Epidemiology of Acute Rheumatic Fever and Rheumatic Heart Disease in Low and Middle-Income Countries. *American Journal of Epidemiology and Infectious Disease*, 1, 34-40.
- TADELE, H., MEKONNEN, W. & TEFERA, E. 2013. Rheumatic mitral stenosis in children: more accelerated course in sub-Saharan patients. *BMC Cardiovasc Disord*, 13, 95.
- TANTCHOU TCHOUMI, J. C. & BUTERA, G. 2009. Rheumatic valvulopathies occurrence, pattern and follow-up in rural area: the experience of the Shisong Hospital, Cameroon. *Bull Soc Pathol Exot*, 102, 155-8.
- TANTCHOU TCHOUMI, J. C. & BUTERA, G. 2013. Profile of cardiac disease in Cameroon and impact on health care services. *Cardiovasc Diagn Ther*, 3, 236-43.
- TAVEL, M. E. 2006. Cardiac auscultation: a glorious past--and it does have a future! *Circulation*, 113, 1255-9.
- TAVEL, M. E. 2010. Cardiac auscultation: a new method for instruction. *Med Educ*, 44, 1132.
- THALJI, N. M., SURI, R. M., GREASON, K. L. & SCHAFF, H. V. 2014. Risk assessment methods for cardiac surgery and intervention. *Nat Rev Cardiol*.
- THE WORLD DEVELOPMENT REPORT ONLINE. 2014. *The world development report online 2014*, [Online]. <http://data.worldbank.org/indicator/SI.POV.GINI/>: The World Bank. Available: <http://data.worldbank.org/indicator/SI.POV.GINI/> [Accessed 12 May 2014].
- THORNE, S., MACGREGOR, A. & NELSON-PIERCY, C. 2006. Risks of contraception and pregnancy in heart disease. *Heart*, 92, 1520-5.
- TIBAZARWA, K. B., VOLMINK, J. A. & MAYOSI, B. M. 2008. Incidence of acute rheumatic fever in the world: a systematic review of population-based studies. *Heart*, 94, 1534-40.
- TUBRIDY-CLARK, M. & CARAPETIS, J. R. 2007. Subclinical carditis in rheumatic fever: a systematic review. *Int J Cardiol*, 119, 54-8.



- UNITED NATIONS DEVELOPMENT PROGRAMME. 2013. *Human Development reports* [Online]. Available: <http://hdr.undp.org/en/content/human-development-report-2013-summary> [Accessed 13 May 2014].
- VANDENBROUCKE, J. P., VON ELM, E., ALTMAN, D. G., GOTZSCHE, P. C., MULROW, C. D., POCKOCK, S. J., POOLE, C., SCHLESSELMAN, J. J. & EGGER, M. 2014. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): Explanation and elaboration. *Int J Surg*, 12, 1500-24.
- VIJAYALAKSHMI, I. B., VISHNUPRABHU, R. O., CHITRA, N., RAJASRI, R. & ANURADHA, T. V. 2008. The efficacy of echocardiographic criterions for the diagnosis of carditis in acute rheumatic fever. *Cardiol Young*, 18, 586-92.
- VISWANATHAN, M., ANSARI, M. T., BERKMAN, N. D., CHANG, S., HARTLING, L., MCPHEETERS, M., SANTAGUIDA, P. L., SHAMLIYAN, T., SINGH, K., TSERTSVADZE, A. & TREADWELL, J. R. 2011. *Assessing the Risk of Bias of Individual Studies in Systematic Reviews of Health Care Interventions* [Online]. Available: [http://www.effectivehealthcare.ahrq.gov/ehc/products/322/998/MethodsGuideforCERs\\_Viswanathan\\_IndividualStudies.pdf](http://www.effectivehealthcare.ahrq.gov/ehc/products/322/998/MethodsGuideforCERs_Viswanathan_IndividualStudies.pdf) [Accessed 12 January 2014].
- VOS, T., FLAXMAN, A. D., NAGHAVI, M., LOZANO, R., MICHAUD, C., EZZATI, M., SHIBUYA, K., SALOMON, J. A., ABDALLA, S., ABOYANS, V., ABRAHAM, J., ACKERMAN, I., AGGARWAL, R., AHN, S. Y., ALI, M. K., ALVARADO, M., ANDERSON, H. R., ANDERSON, L. M., ANDREWS, K. G., ATKINSON, C., BADDOUR, L. M., BAHALIM, A. N., BARKER-COLLO, S., BARRERO, L. H., BARTELS, D. H., BASANEZ, M. G., BAXTER, A., BELL, M. L., BENJAMIN, E. J., BENNETT, D., BERNABE, E., BHALLA, K., BHANDARI, B., BIKBOV, B., BIN ABDULHAK, A., BIRBECK, G., BLACK, J. A., BLENCOWE, H., BLORE, J. D., BLYTH, F., BOLLIGER, I., BONAVENTURE, A., BOUFOUS, S., BOURNE, R., BOUSSINESQ, M., BRAITHWAITE, T., BRAYNE, C., BRIDGETT, L., BROOKER, S., BROOKS, P., BRUGHA, T. S., BRYAN-HANCOCK, C., BUCELLO, C., BUCHBINDER, R., BUCKLE, G., BUDKE, C. M., BURCH, M., BURNEY, P., BURSTEIN, R., CALABRIA, B., CAMPBELL, B., CANTER, C. E., CARABIN, H., CARAPETIS, J., CARMONA, L., CELLA, C., CHARLSON, F., CHEN, H., CHENG, A. T., CHOU, D., CHUGH, S. S., COFFENG, L. E., COLAN, S. D., COLQUHOUN, S., COLSON, K. E., CONDON, J., CONNOR, M. D., COOPER, L. T., CORRIERE, M., CORTINOVIS, M., DE VACCARO, K. C., COUSER, W., COWIE, B. C., CRIQUI, M. H., CROSS, M., DABHADKAR, K. C., DAHIYA, M., DAHODWALA, N., DAMSERE-DERRY, J., DANAEI, G., DAVIS, A., DE LEO, D., DEGENHARDT, L., DELLAVALLE, R., DELOSSANTOS, A., DENENBERG, J., DERRETT, S., DES JARLAIS, D. C., DHARMARATNE, S. D., DHERANI, M., et al. 2012. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet*, 380, 2163-96.
- VUKANOVIC-CRILEY, J. M. C. S., WARDE CM , BOKER JR , GUEVARA-MATHEUS L , CHURCHILL WH , NELSON WP , CRILEY JM 2006. Competency in cardiac examination skills in medical students, trainees, physicians, and faculty: a multicenter study. *Arch Intern Med.*, Mar 27;, 610-6.
- WAGNER, E. H., AUSTIN, B. T., DAVIS, C., HINDMARSH, M., SCHAEFER, J. & BONOMI, A. 2001. Improving chronic illness care: translating evidence into action. *Health Aff (Millwood)*, 20, 64-78.
- WALKER, K. G., HUMAN, D. G., DE MOOR, M. M. & SPRENGER, K. J. 1987. The problem of compliance in rheumatic fever. *S Afr Med J*, 72, 781-3.
- WANG, D., LIU, M., HAO, Z., TAO, W., LIN, S., ZHANG, S., WU, B., MA, Z. & DONG, W. 2012a. Features of acute ischemic stroke with rheumatic heart disease in a hospitalized Chinese population. *Stroke*, 43, 2853-7.
- WANG, D., LIU, M., LIN, S., HAO, Z., TAO, W., CHEN, X., LUAN, R. & DONG, W. 2013. Stroke and rheumatic heart disease: a systematic review of observational studies. *Clin Neurol Neurosurg*, 115, 1575-82.
- WANG, H., DWYER-LINDGREN, L., LOFGREN, K. T., RAJARATNAM, J. K., MARCUS, J. R., LEVIN-RECTOR, A., LEVITZ, C. E., LOPEZ, A. D. & MURRAY, C. J. 2012b. Age-specific and sex-specific mortality in 187 countries, 1970-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet*, 380, 2071-94.

- WATKINS, D. A. & MAYOSI, B. M. 2011. Benzathine penicillin for recurrence of rheumatic fever: the jury is still out. *Pediatr Cardiol*, 32, 247.
- WATKINS, D. A., SEBITLOANE, M., ENGEL, M. E. & MAYOSI, B. M. 2012. The burden of antenatal heart disease in South Africa: a systematic review. *BMC Cardiovasc Disord*, 12, 23.
- WATROUS, R. L., THOMPSON, W. R. & ACKERMAN, S. J. 2008. The impact of computer-assisted auscultation on physician referrals of asymptomatic patients with heart murmurs. *Clin Cardiol*, 31, 79-83.
- WEBB, R. H., WILSON, N. J., LENNON, D. R., WILSON, E. M., NICHOLSON, R. W., GENTLES, T. L., O'DONNELL, C. P., STIRLING, J. W., ZENG, I. & TRENHOLME, A. A. 2011. Optimising echocardiographic screening for rheumatic heart disease in New Zealand: not all valve disease is rheumatic. *Cardiol Young*, 21, 436-43.
- WHO 2004. *Rheumatic Fever and Rheumatic Heart Disease. Report of a WHO Expert Consultation.*
- WHO TECHNICAL REPORT SERIES 2004. *Rheumatic fever and rheumatic heart disease: Report of a WHO expert panel, Geneva 29 October -1 November 2001*, Geneva, WHO.
- WILSON, N. 2008. Echocardiography and subclinical carditis: guidelines that increase sensitivity for acute rheumatic fever. *Cardiol Young*, 18, 565-8.
- WOYWODT, A. H. M., PILZ B, SCHNEIDER W, DIETZ R, LUFT FC. 1999. Cardiopulmonary auscultation: duo for strings-Opus 99. *Arch Intern Med.*, Nov 8;, 2477-9.
- WYBER, R., ZÜHLKE, L. J. & CARAPETIS, J. 2014. The case for global investment in rheumatic heart-disease control. *Bulletin of the World Health Organization*, 92, 768-770.
- YANKAH, C. A., SINIAWSKI, H., DETSCHADES, C., STEIN, J. & HETZER, R. 2011. Rheumatic mitral valve repair: 22-year clinical results. *J Heart Valve Dis*, 20, 257-64.
- YUSUF, S., RANGARAJAN, S., TEO, K., ISLAM, S., LI, W., LIU, L., BO, J., LOU, Q., LU, F., LIU, T., YU, L., ZHANG, S., MONY, P., SWAMINATHAN, S., MOHAN, V., GUPTA, R., KUMAR, R., VIJAYAKUMAR, K., LEAR, S., ANAND, S., WIELGOSZ, A., DIAZ, R., AVEZUM, A., LOPEZ-JARAMILLO, P., LANAS, F., YUSOFF, K., ISMAIL, N., IQBAL, R., RAHMAN, O., ROSENGREN, A., YUSUFALI, A., KELISHADI, R., KRUGER, A., PUOANE, T., SZUBA, A., CHIFAMBA, J., OGUZ, A., MCQUEEN, M., MCKEE, M. & DAGENAIS, G. 2014. Cardiovascular risk and events in 17 low-, middle-, and high-income countries. *N Engl J Med*, 371, 818-27.
- ZHANG, W., MONDO, C., OKELLO, E., MUSOKE, C., KAKANDE, B., NYAKOOJO, W., KAYIMA, J. & FREERS, J. 2013. Presenting features of newly diagnosed rheumatic heart disease patients in Mulago Hospital: a pilot study. *Cardiovasc J Afr*, 24, 28-33.
- ZHOU, X.-H., OBUCHOWSKI, N. A. & MCCLISH, D. K. 2011. *Statistical Methods in Diagnostic Medicine (Wiley Series in Probability and Statistics)*, Wiley.
- ZÜHLKE, L. & MAYOSI, B. M. 2009. The challenge of screening for asymptomatic rheumatic heart disease in South Africa. *SA Heart Journal* 6, 100-103.
- ZÜHLKE, L., MYER, L. & MAYOSI, B. M. 2012a. The promise of computer-assisted auscultation in screening for structural heart disease and clinical teaching. *Cardiovascular journal of Africa*, 23, 1-4.
- ZÜHLKE, L. & MAYOSI, B. M. 2013. Echocardiographic screening for subclinical rheumatic heart disease remains a research tool pending studies of impact on prognosis. *Curr Cardiol Rep*, 15, 343.
- ZÜHLKE, L., MIRABEL, M. & MARIJON, E. 2013. Congenital heart disease and rheumatic heart disease in Africa: recent advances and current priorities. *Heart*, 99, 1554-61.
- ZÜHLKE, L., ENGEL, M. E., KARTHIKEYAN, G., RANGARAJAN, S., MACKIE, P., CUPIDO, B., MAUFF, K., ISLAM, S., JOACHIM, A., DANIELS, R., FRANCIS, V., OGENDO, S., GITURA, B., MONDO, C., OKELLO, E., LWABI, P., AL-KEBSI, M. M., HUGO-HAMMAN, C., SHETA, S. S., HAILEAMLAK, A., DANIEL, W., GOSHU, D. Y., ABDISSA, S. G., DESTA, A. G., SHASHO, B. A., BEGNA, D. M., ELSAYED, A., IBRAHIM, A. S., MUSUKU, J., BODE-THOMAS, F., OKEAHIALAM, B. N., IGE, O., SUTTON, C., MISRA, R., ABUL FADL, A., KENNEDY, N., DAMASCENO, A., SANI, M., OGAI, O. S., OLUNUGA, T., ELHASSAN, H. H., MOCUMBI, A. O., ADEOYE, A. M., MNTLA, P., OJJI, D., MUCUMBITSI, J., TEO, K., YUSUF, S. & MAYOSI, B. M. 2014a. Characteristics, complications, and gaps in evidence-based interventions in rheumatic heart disease: the Global Rheumatic Heart Disease Registry (the REMEDY study). *Eur Heart J*, pii: ehu449. [Epub ahead of print].



- ZÜHLKE, L., WATKINS, D. & ENGEL, M. E. 2014b. Incidence, prevalence and outcomes of rheumatic heart disease in South Africa: a systematic review protocol. *BMJ Open*, 4, e004844-e004844.
- ZÜHLKE, L. J. 2011. Rheumatic heart disease and the asap programme: fresh insights into an old disease. *Continuing medical education journal*, 29, 460-462.
- ZÜHLKE, L. J., KARTHIKEYAN, G., ENGEL, M. E., CUPIDO, B., RANGARAJAN, S., YUSUF, S., TEO, K. & MAYOSI, B. 2012b. The Rheumatic Heart Disease Global Registry (REMEDY) study - Preliminary report. *Circulation*, 125, e723.
- ZÜHLKE, L. J. & STEER, A. C. 2013. Estimates of the Global Burden of Rheumatic Heart Disease. *Global Heart*, 8, 189-195.
- ZÜHLKE, L. J., MAYOSI BM 2009. The challenge of screening for asymptomatic rheumatic heart disease in South Africa. *SA Heart*, 6, 100-103.

## 10 Appendices

Appendix 10.1 University of Cape Town IRB Ethics approval .....	170
Appendix 10.2 MOOSE checklist .....	173
Appendix 10.3 Data extraction form .....	174
Appendix 10.4 Case record form: Study 2 .....	185
Appendix 10.5 Case record form: Study 3 .....	192
Appendix 10.6 Registration form .....	197
Appendix 10.7 REMEDY Baseline form .....	198
Appendix 10.8 List of participating sites and country .....	208
Appendix 10.9 12 and 24 month Follow-up forms .....	210
Appendix 10.10 Manual of operations REMEDY .....	219

Appendix 10.1 University of Cape Town IRB Ethics approval

10.1 CT IRB Ethics approval letters

UNIVERSITY OF CAPE TOWN



Health Sciences Faculty  
Research Ethics Committee  
Room E53-24 Groote Schuur Hospital Old Main Building  
Observatory 7925  
Telephone [021] 406 6338 • Facsimile [021] 406 6411  
e-mail: preaward@clt.uct.ac.za

13 January 2006

REC REF: 028/2006

Prof SM Mayosi  
Department of Medicine

Dear Prof Mayosi

PAN AFRICAN SOCIETY OF CARDIOLOGY RHEUMATIC FEVER/RHEUMATIC HEART DISEASE  
PREVENTION PROGRAMME IN AFRICAN NATIONS: THE ASAP PROJECT

Thank you for submitting your study to the Research Ethics Committee for review. It is a pleasure to inform you that the committee has formally approved the above mentioned study. Authorisation to establish a RF/RHD registry and to establish a South African Demonstration site in Cape Town is granted.

Please quote the REC. REF in all your correspondence.

Yours sincerely

PROF. T ZABOW  
CHAIRPERSON



Köster

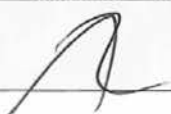


UNIVERSITY OF CAPE TOWN  
UNIVERSITEIT VAN KAAPSTAD

FACULTY OF HEALTH SCIENCES  
Human Research Ethics Committee



### FHS016: Annual Progress Report / Renewal

<b>HREC office use only (FWA00001637; IRB00001938)</b>			
<b>This serves as notification of annual approval, including any documentation described below.</b>			
<input checked="" type="checkbox"/> Approved	Annual progress report	Approved until/next renewal date	30.05.2015
<input type="checkbox"/> Not approved	See attached comments		
Signature Chairperson of the HREC			Date Signed 17/11/2014

Comments to PI from the HREC		HUMAN RESEARCH ETHICS COMMITTEE  17 NOV 2014  HEALTH SCIENCES FACULTY UNIVERSITY OF CAPE TOWN
<b>Principal Investigator to complete the following:</b>		
<b>1. Protocol information</b>		
Date (when submitting this form)	15 November 2014	
HREC REF Number	028/2006	Current Ethics Approval was granted until 30 May 2014
Protocol title	Pna-African Society of Cardiology Rheumatic Fever / Rheumatic Heart Disease Prevention Programme in African Nations : the A.S.A.P. Project	
Protocol number (if applicable)		
Are there any sub-studies linked to this study?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No	
If yes, could you please provide the HREC Ref's for all sub-studies? <b>Note:</b> A separate FHS016 must be submitted for each sub-study.	466/2008 310/2013	
Principal Investigator	Bongani M. Mayosi	
Department / Office Internal Mail Address	Medicine, J Floor, OMB	

1.1 Does this protocol receive US Federal funding?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
1.2 If the study receives US Federal Funding, does the annual report require full committee approval?	<input type="checkbox"/> Yes	<input type="checkbox"/> No
1.3 Has sponsorship of this study changed? If yes, please attach a revised summary of the budget.	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No



**UNIVERSITY OF CAPE TOWN**  
**Faculty of Health Sciences**  
**Human Research Ethics Committee**



Room E52-24 Old Main Building  
Groote Schuur Hospital  
Observatory 7925  
Telephone [021] 406 6338 • Facsimile [021] 406 6411  
Email: [jamees.emjedi@uct.ac.za](mailto:jamees.emjedi@uct.ac.za)  
Website: [www.health.uct.ac.za/fhs/research/humanethics/forms](http://www.health.uct.ac.za/fhs/research/humanethics/forms)

26 January 2015

**HREC REF: 028/2006**

**Dr L Zülke**  
Medicine

Dear Zülke

**PROJECT TITLE: THE OUTCOMES OF ASYMPTOMATIC AND SYMPTOMATIC RHEUMATIC HEART DISEASE". RESULTS OF REGISTRY AND DEMONSTRATION SITE.**

This letter confirms that Dr Liesl Zülke is also involved in this study as has been listed as a co-investigator on the above-mentioned study.

**Approval is granted for one year until 30 May 2015.**

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

**Please quote the HREC reference no in all your correspondence.**

Yours sincerely

**PROFESSOR M. BLOCKMAN**  
**CHAIRPERSON, FHS HUMAN ETHICS**

## 10.2 Study 1: Meta-analysis of Observational Studies in Epidemiology (MOOSE) checklist

	Reported on page	Comments
<b>Reporting of background should include</b>		
Problem definition	43, Section 2.2	Protocol previously published
Hypothesis statement	44, Section 2.2	Protocol previously published
Description of study outcomes	50	Section 2.2.9
Type of exposure or intervention used	43-44	Section 2.2
Type of study designs used	43-44	Section 2.2.2
Study population	44	Section 2.2.2
<b>Reporting of search strategy should include</b>		
Qualifications of searchers (e.g. librarians and investigators)	45	Section 2.2.3
Search strategy, including time period used in the synthesis and key words	46	Tables 2.1 & 2.2
Effort to include all available studies, including contact with authors	46	Section 2.2.3
Databases and registries searched	46	Section 2.2.3
Search software used, name and version, including special features used (e.g. explosion)	46	Section 2.2.3
Use of hand searching (e.g. reference lists of obtained articles)	46	Section 2.2.3
List of citations located and those excluded, including justification	70	Section 3.4, Figure 3.1, Table 3.1
Method of addressing articles published in languages other than English	45	Section 2.2.3
Method of handling abstracts and unpublished studies	45	Section 2.2.3
Description of any contact with authors	45	Section 2.2.3
<b>Reporting of methods should include</b>		
Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	42	Protocol previously published
Rationale for the selection and coding of data (e.g. sound clinical principles or convenience)	45	Protocol previously published

Documentation of how data were classified and coded (e.g. multiple raters, blinding and interrater reliability)	45	Protocol previously published
Assessment of confounding (e.g. comparability of cases and controls in studies where appropriate)	NA	
Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results	48	Section 2.2.5, Table 3.2,
Assessment of heterogeneity	88	Discussion, Figures 3.4 and 3.5,
Description of statistical methods (e.g. complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	50	Section 2.2.7
Provision of appropriate tables and graphics	Throughout	Section 2.2, Chapter 3
<b>Reporting of results should include</b>		
Graphic summarizing individual study estimates and overall estimate	Throughout	Section 2.2, Chapter 3
Table giving descriptive information for each study included	73-75	Table 3.2, 3.3 and 3.4.
Results of sensitivity testing (e.g. subgroup analysis)	NA	
Indication of statistical uncertainty of findings	NA	
<b>Reporting of discussion should include</b>		
Quantitative assessment of bias (e.g. publication bias)	74, 76-77	Table 3.2 and 3.3
Justification for exclusion (e.g. exclusion of non-English language citations)	71	Table 3.1
Assessment of quality of included studies	73	Table 3.2
<b>Reporting of conclusions should include</b>		
Consideration of alternative explanations for observed results	87	Limitations
Generalization of the conclusions (e.g. appropriate for the data presented and within the domain of the literature review)	88	Conclusions
Guidelines for future research	88	Implications for research
Disclosure of funding source	v	No funding for this particular study, funding for thesis period listed in acknowledgments.

### Appendix 10.3 Data extraction form

### 10.3 Study 1: Data extraction form

- Be consistent in the order and style you use to describe the information for each report.
- Record any missing information as unclear or not described, to make it clear that the information was not found in the study report(s), not that you forgot to extract it.

Review title	
Study ID ( <i>surname of first author and year first full report of study was published e.g. Smith 2001</i> )	
Study number	
Notes	

#### General Information

Date form completed ( <i>dd/mm/yyyy</i> )	
Name/ID of person extracting data	
Full references citation: Author, Journal, Title	
Study author contact details	
Publication type ( <i>e.g. full report, abstract, letter</i> )	
City/province of origin	
Notes:	

#### Study eligibility

Study Characteristics	Eligibility criteria	Eligibility criteria met?			Location in text or source ( <i>pg &amp; ¶/fig/table</i> )
		Yes	No	Unclear	
Type of study	Case series	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
	Retrospective cohort	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
	Prospective cohort	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
	Cross-sectional study	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Participants and setting	South African patients 1994-2014	<input type="checkbox"/>			
RHD case definition	Auscultation/clinical	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
	Echocardiography	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
	Chart review	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	



	Pathology	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	
	Not specified	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	
Types of outcome measures	incidence	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	
	prevalence	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	
	remission rate	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	
	relative risk of mortality (i.e., excess mortality)	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	
	cause-specific mortality	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	
	heart failure	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	
	ischaemic/thromboembolic or haemorrhagic stroke	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	
	atrial fibrillation	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	
	infective endocarditis	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	
	valve repair or replacement..	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	
Study Characteristics	Eligibility criteria	Eligibility criteria met? Y N U	Location in text or source (pg & ¶ / fig / table)
Outcome measures	1) Incidence 2) prevalence; 3) Secondary outcomes	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	
		<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	
		<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	
INCLUDE <input type="checkbox"/> EXCLUDE <input type="checkbox"/>			
Reason for exclusion			
Notes:			

**DO NOT PROCEED IF STUDY EXCLUDED FROM REVIEW**

## Characteristics of included studies

### Methods

	Descriptions as stated in report/paper	Location in text or source ( <i>pg &amp; ¶/fig/table</i> )
<b>Aim of study</b>		
<b>Design</b>		
<b>Unit of observation</b>		
<b>Start date</b>		
<b>End date</b>		
<b>Duration of participation</b> <i>(from recruitment to last follow-up)</i>		
<b>Ethical approval needed/ obtained for study</b>	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unclear	
<b>Notes:</b>		

### Participants

	Description	Location in text or source ( <i>pg &amp; ¶/fig/table</i> )
<b>Population description</b> <i>(from which study participants are drawn)</i>		
<b>Setting and context</b>		
<b>Inclusion criteria</b>		
<b>Exclusion criteria</b>		
<b>Method of recruitment of participants</b>		

Informed consent obtained	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unclear		
Total no. of subjects			
Number of total person-years (if applicable)			
Missing data			

Epidemiological studies

Outcome(s)  Definition, measure & classification	Primary outcome –		
	<input type="checkbox"/> Incidence		
	<input type="checkbox"/> Prevalence		
	<input type="checkbox"/> Mortality		
Number in reference population	<input type="checkbox"/> Census tract <input type="checkbox"/> Hospital catchment <input type="checkbox"/> Other <input type="checkbox"/> not provided		
Age stratum	Crude Value	Proportional/weighted value	

Comments on above Eg, methods of stratification/aggregation		
Morbidity Studies		
Outcome(s) Definition, measure & classification	Primary outcome –  <input type="checkbox"/> heart failure	
	<input type="checkbox"/> Infective endocarditis	
	<input type="checkbox"/> stroke/TIA	
	<input type="checkbox"/> Atrial fibrillation	
	<input type="checkbox"/> Mortality	
	<input type="checkbox"/> autopsy/necropsy	
Total RHD cases	<input type="checkbox"/> Pure MS-----n= <input type="checkbox"/> Pure MR-----n= <input type="checkbox"/> Combined-----n= <input type="checkbox"/> Lesions not specified---n=	
Case fatality rate <hr/>	 -----  <input type="checkbox"/> Not provided	
Additional comments		
Authors' reported limitations of study's methods/results	<input type="checkbox"/> Mortality	
Results (specify, e.g. OR, RR, IRR) (specify the reference group)	Crude	

	Adjusted
--	----------

Surgical Studies

Outcome(s) Definition, measure & classification	Primary intervention –						
	<input type="checkbox"/> MVR						
	<input type="checkbox"/> AVR						
	<input type="checkbox"/> TVR						
	<input type="checkbox"/> M-plasty						
	<input type="checkbox"/> A-plasty						
	<input type="checkbox"/> T plasty						
	<input type="checkbox"/> percutaneous						
	<input type="checkbox"/> other						
Primary surgical pathology	<input type="checkbox"/> Pure MS.-----n= <input type="checkbox"/> Pure MR-----n= <input type="checkbox"/> Combined-----n= <input type="checkbox"/> Lesions not specified---n=						
Indication for surgery	<input type="checkbox"/> acute carditis/failure <input type="checkbox"/> chronic failure <input type="checkbox"/> infection <input type="checkbox"/> not provided						
Outcome	Rate/pt-yr	#non-fatal	# fatal	% CFR	Other parameter describe	pg	
Valve failure							
Iscahemic CVA							

Hameorrhagic CVA						
Systemic Embolism						
Major bleeding						
PVThrombosis						
Infective endocarditis						
Re-operation						
Additional comments						
Authors' reported limitations of study's methods/results	<input type="checkbox"/> Mortality					
Probability of event-free survival						
Generalised mortality rate						
Other observations/outcomes						
Comments						

### Quality assessment

<b>Representativeness of the cases to the general population with RHD</b>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	1	2	3	4 ( 4 being the highest score)
<b>Completeness of dataset (including follow-up)</b>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	1	2	3	4 ( 4 being the highest score)

validity of case definitions and methods of ascertainment	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4 ( 4 being the highest score)
Appropriateness of the study design to the research question.	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4 ( 4 being the highest score)
population-based study	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Unclear, If Yes-> A in next block	
hospital-based study accounting for catchment area	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Unclear If Yes-> B in next block	
rates of hospitalization as incidence	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Unclear If Yes-> C in next block	

Other information

<b>Study funding sources</b> <i>(including role of funders)</i>		
<b>Possible conflicts of interest</b> <i>(for study authors)</i>		
	<b>Description as stated in report/paper</b>	<b>Location in text or source</b>
<b>Key conclusions of study authors</b>		
<b>References to other relevant studies</b>		
<b>Correspondence required for further study information</b> <i>(from whom, what and when)</i>		
<b>Notes:</b>		

Risk of bias	Criterion	Cohort	Mark Y/N	Case- Control	Mark Y/N	Case series	Mark Y/N	Cross - sectional	Mark Y/N
Selection bias	Were participants analysed within the groups they were originally assigned to?	x							
	Did the study apply inclusion/exclusion criteria uniformly to all comparison groups?	x						x	
	Were cases and controls selected appropriately (e.g., appropriate diagnostic criteria or definitions, equal application of exclusion criteria to case and controls, sampling not influenced by exposure status)			x					
	Did the strategy for recruiting participants into the study differ across study groups?	x							
	Does the design or analysis control account for important confounding and modifying variables through matching, stratification, multivariable analysis, or other approaches?	x		x		x		x	
Performance bias	Did researchers rule out any impact from a concurrent intervention or an unintended exposure that might bias results?	x		x		x		x	
	Did the study maintain fidelity to the intervention protocol?	x		x		x			
Attrition bias	If attrition (overall or differential nonresponse, dropout, loss to follow-up, or exclusion of participants) was a concern, were missing data handled appropriately (e.g., intention-to-treat analysis and imputation)?	x		x		x		x	
Detection bias	In prospective studies, was the length of follow-up different between the groups, or in case-control studies, was the time period between the intervention/exposure and outcome the same for cases and controls?	x		x					
	Were the outcome assessors blinded to the intervention or exposure status of participants?	x		x		x		x	
	Were interventions/exposures assessed/defined using valid and reliable measures, implemented consistently across all study participants?	x		x		x		x	
	Were outcomes assessed/defined using valid and reliable measures, implemented consistently across all study participants?	x		x		x		x	
	Were confounding variables assessed using valid and reliable measures, implemented consistently across all study participants?	x		x		x		x	
Reporting bias	Were the potential outcomes prespecified by the researchers? Are all prespecified outcomes reported?	x		x		x		x	



**TABLE 2: QUALITY SCORE CRITERIA**

<p><b>1. Study design (selection score)</b></p> <p><b>a.</b> Prospective clinical studies (any type)</p> <ul style="list-style-type: none"> <li>– Consecutive enrolment</li> <li>– Unspecified/random enrolment</li> </ul> <p><b>b.</b> Autopsy studies</p> <ul style="list-style-type: none"> <li>– Consecutive enrolment</li> <li>– Unspecified/random enrolment</li> </ul> <p><b>c.</b> Retrospective reviews (including subgroup analysis)</p> <p><b>d.</b> Review/editorial</p> <p><b>e.</b> Case report</p>	<p>2</p> <p>1</p> <p>2</p> <p>1</p> <p>1</p> <p>0</p> <p>0</p>
<p><b>2. Study objectives (selection score)</b></p> <p><b>a.</b> Clear inclusion criteria</p> <ul style="list-style-type: none"> <li>– Aim related to prevalence or outcomes</li> <li>– Related to /general morbidity/ but not specific to</li> <li>– Unrelated to clinical prevalence</li> </ul> <p><b>b.</b> Unclear inclusion criteria</p>	<p>3</p> <p>2</p> <p>1</p> <p>1</p>
<p><b>3. Diagnosis* (quality of outcome ascertainment)</b></p> <p><b>a.</b> Laboratory-confirmed (any specified method/specimen)</p> <p><b>b.</b> Clinical case definition (consistent with WHO guidelines)</p> <p><b>c.</b> Not specified</p>	<p>2</p> <p>1</p> <p>0</p>
<p><b>4. Denominator</b></p> <p><b>a.</b> Raw data denominator</p> <p><b>b.</b> Calculated denominator</p> <p><b>c.</b> No/unclear denominator/investigated &lt; 20% of cohort for/exclusion group</p>	<p>2</p> <p>1</p> <p>0</p>
<p><b>5. Numerator (numbers)</b></p> <p><b>a.</b> Raw data numerator</p> <p><b>b.</b> Calculated numerator</p> <p><b>c.</b> No/unclear numerator (clinical not mentioned/tested)</p>	<p>2</p> <p>1</p> <p>0</p>
<p><b>6. Assessment of bias (low, high or unclear risk<sup>^</sup>)</b></p> <p><b>a.</b> Attrition bias</p> <ul style="list-style-type: none"> <li>– Amount, nature or handling of incomplete outcome data</li> </ul> <p><b>b.</b> Selection bias</p> <ul style="list-style-type: none"> <li>– Representativeness of the cases/cohort (clear reasons for and rates of non-inclusion)</li> </ul>	

## Appendix 10.4 Case record form: Study 2

## 10.4 Study 2: Case record form

CT (GERHD) CRF, Version: 1.1

Updated Jan 2014

Participant No.: \_\_\_\_\_

**CASE RECORD FORM**  
**RHEUMATIC HEART DISEASE**  
**FOLLOW-UP EXAMINATION**

**PARTICIPANT NUMBER:** \_\_\_\_\_

**DIAGNOSTIC CATEGORY: (CIRCLE ONE ONLY)** To be completed at end of today's examination

- |  |      |
|--|------|
| Known diagnosis of Chronic Rheumatic Heart Disease | = 01 |
| School screening – normal                          | = 02 |
| School screening –borderline rheumatic             | = 03 |
| School screening - 1st diagnosis of Chronic RHD    | = 04 |
| School screening – Other (Specify _____)           | = 05 |
| Family screening - normal                          | = 06 |
| Family screening - abnormal                        | = 07 |

MODE OF DIAGNOSIS: ☐ School screening  
☐ Family screening

**DATE:** \_\_\_\_\_

**SIGNED:** \_\_\_\_\_

**DESIGNATION:** \_\_\_\_\_

**HISTORY/AUSCULTATION****PART IA. CONSENT AND ANTHROPOMETRIC MEASUREMENTS**

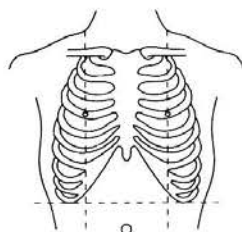
1. Participant Number	I C I T H _ _ _ _ _		
2. Initials:	_ _ _ / _ _ _		
3. Site:	Name _____		
4. Site	Number _ _ _		
5. Date of Enrolment:	_ _ _ / _ _ _ / <u>2011</u> _ _ dd mm yyyy		
6. Informed consent obtained?	<input type="checkbox"/> Yes <input type="checkbox"/> No <b>IF NO DO NOT CONTINUE</b> If no; why not _____		
7. Height _ _ _ . _ _	8. Weight _ _ _ . _ _	9. AGE _ _	
10. DOB _ _ _ / _ _ _ / _ _ _			

**PART IB. HISTORY**

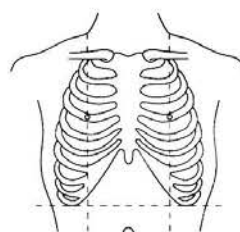
1. Past medical History
2. History of sore throat/ARF
3. Family History esp any cardiac history
4. Any other history of note
Current contact details:
Current contact details:

**PART IC. RHD CARDIAC EXAMINATION / AUSCULTATION ASSESSMENT****16. Is there a murmur?**☐ Yes → go to 17☐ No**17. What is the nature of the murmur?**1. ☐ Systolic →a. ☐ PSMb. ☐ ESM2. ☐ Diastolic3. ☐ Thrill4. ☐ Radiation5. ☐ Other → \_\_\_\_\_

Cardiac Impulse and Thrills



Heartsounds and Murmurs



ABDOMEN:

**18. Your diagnosis?**1. ☐ Innocent2. ☐ Pathological (if pathological tick all that apply) →☐ MR☐ MS☐ AR☐ AS☐ VSD☐ Other \_\_\_\_\_3. ☐ Not sure**19. Are there additional abnormalities?**

1. Displaced Apex beat

☐ Yes☐ No

2. Bibasal Crepitations

☐ Yes☐ No

3. Evidence of PHT

☐ Yes☐ No

4. Presence of Hepatomegaly

☐ Yes☐ No

5. Effort intolerance on direct questioning

☐ Yes☐ No

CT (GERHD) CRF, Version: 1.1		Updated Jan 2014		Participant No.:	
------------------------------	--	------------------	--	------------------	--

20. Other findings and action:

21. Signed: \_\_\_\_\_

Person completing section

22. Date: |\_|\_|/|\_|/|2|0|0|\_|\_|

ddmmyyyy

CT (GERHD) CRF, Version: 1.1

Updated Jan 2014

Participant No.:

--	--	--	--	--	--	--	--

Pt ID

y	y	y	y	m	m	d	d
---	---	---	---	---	---	---	---

date

Quality of Imaging: ☐ poor ☐ adequate ☐ good

**Morphology**

**i) Mitral Valve Morphology**

Normal ☐

Abnormal ☐

Elbow deformity of AMVL ☐

Thickened AMVL ☐

Tethered or restricted AMVL ☐

Thickened PMVL ☐

Tethered PMVL ☐

Elongation of AMVL chordae ☐

Rupture of AMVL chordae ☐

Flail AMVL or PMVL ☐

Calcification ☐

Vegetations ☐

Nodules ☐

Abnormal Submitral apparatus ☐

Prolapse/hypermobility AMVL or PMVL ☐

Yes


Long-axis parasternal

AMVL at margin ☐ mm

AMVL at midleaflet ☐ mm

4 Chamber

AMVL at margin ☐ mm

AMVL at midleaflet ☐ mm

**ii) Aortic Valve Morphology**

Normal ☐

Abnormal ☐

Thickened valve cusps ☐

Coaptation defect ☐

Commissural fusion ☐

Calcification ☐

Vegetations ☐

Nodules ☐

Prolapse ☐

Yes


Short axis

Non-coronary ☐ mm

Left coronary ☐ mm

Right coronary ☐ mm

**iii) Pulmonary Valve Morphology**

Normal ☐

Abnormal ☐

Calcification ☐

Vegetations ☐

Nodules ☐

**iv) Tricuspid Valve Morphology**

Normal ☐

Abnormal ☐

Calcification ☐

Vegetations ☐

Nodules ☐

**v) Measurements**

A.S.A.P. FOLLOW-UP CLINIC: Case Report Form

p5/7

IVS(ed)	<table border="1"><tr><td></td><td></td></tr><tr><td></td><td></td></tr></table>					.	<table border="1"><tr><td></td></tr><tr><td></td></tr></table>			LVSF%	<table border="1"><tr><td></td><td></td></tr><tr><td></td><td></td></tr></table>					.	<table border="1"><tr><td></td></tr><tr><td></td></tr></table>			LA	<table border="1"><tr><td></td><td></td></tr></table>		
LVEDD	<table border="1"><tr><td></td><td></td></tr><tr><td></td><td></td></tr></table>					.	<table border="1"><tr><td></td></tr><tr><td></td></tr></table>			PWL V(ed)	<table border="1"><tr><td></td><td></td></tr><tr><td></td><td></td></tr></table>					.	<table border="1"><tr><td></td></tr><tr><td></td></tr></table>						
LVESD	<table border="1"><tr><td></td><td></td></tr><tr><td></td><td></td></tr></table>					.	<table border="1"><tr><td></td></tr><tr><td></td></tr></table>			LA:AO ratio	<table border="1"><tr><td></td><td></td></tr><tr><td></td><td></td></tr></table>					.	<table border="1"><tr><td></td></tr><tr><td></td></tr></table>						

**vi) Doppler Evaluation: Mitral Valve**

Regurgitation

Absent 

--

Present 

--

➤

Seen in at least 2 views

In at least one view jet length > 2 cm

Vmax>3m/sec

Pan-systolic jet(at least 1 tracing)

Yes


Stenosis

Absent 

--

Present 

--

➤

Mean gradient(mmHg)

MVA in cm<sup>2</sup>

Vmax>3m/sec

TR jet(mmHg)



**vi) Doppler Evaluation: Aortic Valve**

Regurgitation

Absent 

--

Present 

--

➤

Seen in at least 2 views

In at least one view jet length > 1 cm

Vmax in early diastole>3m/sec

Halodiastolic jet(at least 1 tracing)

Yes


Stenosis

Absent 

--

Present 

--



➤

Mean gradient(mmHg)



Peak velocity( mmHg)



vi) Doppler Evaluation: Pulmonary Valve

<b>Regurgitation</b>		<b>Stenosis</b>	
Absent	<input type="checkbox"/>	Absent	<input type="checkbox"/>
Present	<input type="checkbox"/> Yes	Present	<input type="checkbox"/>
			
Mild/Physiological	<input type="checkbox"/>	Mean gradient(mmHg)	<input type="text"/> <input type="text"/> . <input type="text"/>
Severe	<input type="checkbox"/>	Peak velocity( mmHg)	<input type="text"/> <input type="text"/> . <input type="text"/>

vii) Doppler Evaluation: Tricuspid Valve

<b>Regurgitation</b>		<b>Stenosis</b>	
Absent	<input type="checkbox"/>	Absent	<input type="checkbox"/>
Present	<input type="checkbox"/> Yes	Present	<input type="checkbox"/>
			
Mild/Physiological	<input type="checkbox"/>	Mean gradient(mmHg)	<input type="text"/> <input type="text"/> . <input type="text"/>
Severe	<input type="checkbox"/>	Peak velocity( mmHg)	<input type="text"/> <input type="text"/> . <input type="text"/>

viii) Chambers

	Normal	Thrombus	
Right Atrium:	<input type="checkbox"/>	<input type="checkbox"/>	
Right Ventricle:	<input type="checkbox"/>	<input type="checkbox"/>	
Left Atrium:	<input type="checkbox"/>	<input type="checkbox"/>	
Left Ventricle:	<input type="checkbox"/>	<input type="checkbox"/>	
Pericardium:	<input type="checkbox"/> Effusion	<input type="checkbox"/> Calcification	<input type="checkbox"/> Thickened <input type="checkbox"/>

**FINAL IMPRESSION**

**Definite RHD:**

A) At <u>least two</u> morphological feature RHD of the MV <u>and</u> pathological MR or	<input type="checkbox"/>
B) MS ( $\geq$ to 4 mmHg)	<input type="checkbox"/>
C) At <u>least one</u> morphological feature RHD of the AV <u>and</u> pathological AR	<input type="checkbox"/>
D. Borderline disease of <u>both</u> the mitral and aortic valves	<input type="checkbox"/>

**Borderline RHD :**

A) At least two morphological features of RHD of the MV	<input type="checkbox"/>
B) Pathological MR or MS (2 – 3.9 mmHg) without morphological change of RHD	<input type="checkbox"/>
C) Pathological AR without morphological change of RHD	<input type="checkbox"/>

**Other:**

A) Congenital Heart Disease	<u>Details</u>	<input type="checkbox"/>
B) Acquired Heart Disease	<u>Details</u>	<input type="checkbox"/>

<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
----------------------	----------------------	----------------------	----------------------	----------------------	----------------------	----------------------	----------------------	----------------------

Last name/Initial	Signature	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
-------------------	-----------	----------------------	----------------------	----------------------	----------------------	----------------------	----------------------	----------------------	----------------------	----------------------	----------------------	----------------------	----------------------



## 10.5 Study 3: Case record form

### RHEUMATIC HEART DISEASE FOLLOW-UP EXAMINATION

**PARTICIPANT NUMBER:** \_\_\_\_\_

**ECHO NUMBER:** \_\_\_\_\_

**DIAGNOSTIC CATEGORY: (CIRCLE ONE ONLY)** to be completed at end of today's examination

School screening – normal = 1

School screening – borderline rheumatic = 2

School screening – definite rheumatic = 3

Referral form completed for sec prophylaxis ☐ Yes ☐ No

Known diagnosis of Chronic Rheumatic Heart Disease = 4

School screening – Other (Specify \_\_\_\_\_) = 5

1. Initials: I\_\_I\_\_I / I\_\_I\_\_I

2. Date of original Enrolment: I\_\_I\_\_I / I\_\_I\_\_I / I2I0I1I\_\_I

3. Date of current Enrolment: I\_\_I\_\_I / I\_\_I\_\_I / I2I0I1I\_\_I

4 Copy of Informed consent? ☐ Yes ☐ No

5. Height I\_\_I\_\_I.I\_\_I 6. Weight I\_\_I\_\_I.I\_\_I 7. AGE I\_\_I

### CONSENT AND ANTHROPOMETRIC MEASUREMENTS

**DATE:** \_\_\_\_\_

**SIGNED:** \_\_\_\_\_

**Subject's contact details:**

a) Name: \_\_\_\_\_  
                                     *Given name*                                    *Surname*

b) Hospital #: 

--	--	--	--	--	--	--	--	--	--

  
                                     → Please fill left to right

c) Home address: \_\_\_\_\_  
                                     *House No.*                                    *Street*                                    *Postal/Zip Code/Box No.*

\_\_\_\_\_  
                     *Town/City*                                    *Province/State*                                    *Country*                                    *GPS Coordinates.*

Home #: \_\_\_\_\_ Work #: \_\_\_\_\_

Cell #: \_\_\_\_\_ E-mail: \_\_\_\_\_

**d) Contact person (Primary):****e) Contact person (Secondary):**

\_\_\_\_\_  
                     *First Name*                    *Last Name*

\_\_\_\_\_  
                     *First Name*                    *Last Name*

Relationship: \_\_\_\_\_

Relationship: \_\_\_\_\_

Home #: \_\_\_\_\_

Home #: \_\_\_\_\_

Cell #: \_\_\_\_\_

Cell #: \_\_\_\_\_

Work #: \_\_\_\_\_

Work #: \_\_\_\_\_

E-mail: \_\_\_\_\_

E-mail: \_\_\_\_\_

**f) Local Physician/Clinic:**

Name: \_\_\_\_\_ Phone: \_\_\_\_\_  
                     *Last name*                    *First name*

Address: \_\_\_\_\_  
                     *Town/City*                    *Province/State*                    *Country*

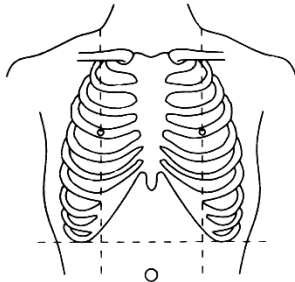
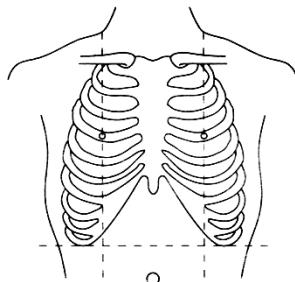
**Springer auscultation:**

- ☐ Not done  
☐ Done

**CAA auscultation:**

- ☐ Not done  
☐ Normal ☐ Abnormal murmur

**RHD CARDIAC EXAMINATION**

1. Is there a murmur? <input type="checkbox"/> Yes <input type="checkbox"/> No	
2. If yes, what is the nature of the murmur? 1. <input type="checkbox"/> Systolic → a. <input type="checkbox"/> PSM b. <input type="checkbox"/> ESM 2. <input type="checkbox"/> Diastolic 3. <input type="checkbox"/> Thrill 4. <input type="checkbox"/> Radiation 5. <input type="checkbox"/> Other → _____	
<p>Cardiac Impulse and Thrills</p>  <p>ABDOMEN:</p>	<p>Heartsounds and Murmurs</p> 
3. Your diagnosis? 1. <input type="checkbox"/> Innocent 2. <input type="checkbox"/> Pathological (if pathological tick all that apply) <input type="checkbox"/> MR → <input type="checkbox"/> MS 3. <input type="checkbox"/> Not sure <input type="checkbox"/> AR <input type="checkbox"/> AS <input type="checkbox"/> VSD <input type="checkbox"/> Other _____	

**4. Are there additional abnormalities?**

☐ Yes ☐ No

If yes, \_\_\_\_\_

**V SCAN EXAMINATION:****PLAX views****Parasternal long axis view color Doppler mode MV**

☐ Normal

☐ colour jet MV < 2 cm ☐ colour jet MV ≥ 2 cm

**V Scan:**

☐ Not done ☐ Number

☐ Normal ☐ Definite (Colour jet ≥ 2 cm)

**Parasternal long axis view 2-D MV and AV**

☐ Normal

☐ morphological abnormalities MV

☐ morphological abnormalities AV

**Parasternal long axis view color Doppler mode AV**

☐ Normal

☐ colour jet AV < 1 cm ☐ colour jet ≥ 1 cm

**PSAX views****Parasternal short axis view 2-D MV level**

☐ Normal

☐ morphological abnormalities MV

**Parasternal short axis view colour MV level**

☐ Normal

☐ colour jet MV < 2 cm ☐ colour jet ≥ 2 cm

**Parasternal short axis view 2-D AV level**

☐ Normal

☐ morphological abnormalities AV

**Parasternal short axis view colour AV level**

☐ Normal

☐ colour jet AV < 1 cm ☐ colour jet ≥ 1 cm

**FULL ECHO EXAMINATION:****Pathological Regurgitation MV**

## Appendices

- ☐ Seen in 2 views
- ☐ In at least one jet length  $\geq 2$  cm
- ☐ Peak velocity  $> 3$  m/s
- ☐ Pansystolic jet in at least one envelope

### **Morphological features MV**

- ☐ AMVL thickening  $\geq 3$  mm (age specific)
- ☐ Chordal thickening
- ☐ Restricted leaflet motion
- ☐ Excessive leaflet tip during systole

### **Pathological Regurgitation AV**

- ☐ Seen in 2 views
- ☐ In at least one jet length  $\geq 1$  cm
- ☐ Early velocity  $\geq 3$  m/s
- ☐ Pansystolic jet in at least one envelope

### **Morphological features features of AV**

- ☐ Irregular or focal thickening
- ☐ Coaptation defect
- ☐ Restricted leaflet motion
- ☐ Prolapse

### **Normal Echocardiographic findings (all of A, B, C or D)**

- ☐ A] MR that does not meet all four Doppler criteria (physiological MR)
- ☐ B] AR that does not meet all four Doppler criteria (physiological AR)
- ☐ C] An isolated morphologic feature of RHD of the MV and/or the AV  
e.g valvar thickening without any associated pathologic stenosis or regurgitation
- ☐ D] Congenital or degenerative valve disease
- ☐ If D \_\_\_\_\_

### **Definite (either A, B, C or D)**

- ☐ A] Pathologic MR **AND** at least 2 morphologic features of RHD of the MV
- ☐ B] MS mean gradient  $> 4$  mmHg
- ☐ C] Pathologic AR and at least 2 morphologic features of RHD of the AV
- ☐ D] Borderline disease of both AV and MV

### **Borderline (either A, B or C)**

- ☐ A] At least two morphologic features of the MV without pathologic MR or MS
- ☐ B] Pathologic MR
- ☐ C] Pathologic AR

## Appendix 10.6 Registration form

## 10.6 Study 4: REMEDY Registration Form

Registration															Page 2				
DataFax #164					Plate #002					Visit #001									
<b>Subject ID</b> <div style="display: flex; justify-content: space-around;"> <div style="border: 1px solid black; width: 30px; height: 20px; display: inline-block;"></div> <div style="border: 1px solid black; width: 30px; height: 20px; display: inline-block;"></div> <div style="border: 1px solid black; width: 30px; height: 20px; display: inline-block;"></div> <div style="border: 1px solid black; width: 30px; height: 20px; display: inline-block;"></div> </div> <div style="display: flex; justify-content: space-around; font-size: small;"> <span>Centre#</span> <span>Subject #</span> </div>										<b>Subject Initials</b> <span style="border: 1px solid black; width: 30px; height: 20px; display: inline-block;"></span> <span style="border: 1px solid black; width: 30px; height: 20px; display: inline-block;"></span> <span style="border: 1px solid black; width: 30px; height: 20px; display: inline-block;"></span> <div style="display: flex; justify-content: space-around; font-size: x-small;"> <span>F</span> <span>M</span> <span>L</span> </div>									
<b>Subject's contact details:</b>																			
<b>a) Name:</b> _____ <div style="display: flex; justify-content: space-around; font-size: x-small;"> <span>Given name</span> <span>Surname</span> </div>																			
<b>b) Hospital #:</b> <span style="border: 1px solid black; width: 30px; height: 20px; display: inline-block;"></span> <span style="border: 1px solid black; width: 30px; height: 20px; display: inline-block;"></span> <span style="border: 1px solid black; width: 30px; height: 20px; display: inline-block;"></span> <span style="border: 1px solid black; width: 30px; height: 20px; display: inline-block;"></span> <span style="border: 1px solid black; width: 30px; height: 20px; display: inline-block;"></span> <span style="border: 1px solid black; width: 30px; height: 20px; display: inline-block;"></span> <span style="border: 1px solid black; width: 30px; height: 20px; display: inline-block;"></span> <span style="border: 1px solid black; width: 30px; height: 20px; display: inline-block;"></span> <div style="text-align: center; font-size: x-small;">       Please fill left to right     </div>																			
<b>c) Home address:</b> _____ <div style="display: flex; justify-content: space-around; font-size: x-small;"> <span>House No.</span> <span>Street</span> <span>Postal/Zip Code/Box No.</span> </div>																			
Town/City				Province/State				Country				GPS Coordinates							
Home #: _____							Work #: _____												
Cell #: _____							E-mail: _____												
<div style="display: flex; justify-content: space-between;"> <div style="width: 48%;"> <b>d) Contact person (Primary):</b>  <div style="display: flex; justify-content: space-around; font-size: x-small;"> <span>First Name</span> <span>Last Name</span> </div> Relationship: _____  Home #: _____  Cell #: _____  Work #: _____  E-mail: _____ </div> <div style="width: 48%;"> <b>e) Contact person (Secondary):</b>  <div style="display: flex; justify-content: space-around; font-size: x-small;"> <span>First Name</span> <span>Last Name</span> </div> Relationship: _____  Home #: _____  Cell #: _____  Work #: _____  E-mail: _____ </div> </div>																			
<b>f) Local Physician/Clinic:</b> Name: _____ <div style="display: flex; justify-content: space-around; font-size: x-small;"> <span>Last name</span> <span>First name</span> </div> Phone: _____																			
Address: _____ <div style="display: flex; justify-content: space-around; font-size: x-small;"> <span>Town/City</span> <span>Province/State</span> <span>Country</span> </div>																			
<div style="display: flex; justify-content: space-between;"> <div style="width: 55%;">           Person Completing Report: _____  <div style="text-align: center; font-size: x-small;">Print last name, first initial</div> </div> <div style="width: 40%;">           Date: <span style="border: 1px solid black; width: 30px; height: 20px; display: inline-block;"></span> <span style="border: 1px solid black; width: 30px; height: 20px; display: inline-block;"></span> <span style="border: 1px solid black; width: 30px; height: 20px; display: inline-block;"></span> <span style="border: 1px solid black; width: 30px; height: 20px; display: inline-block;"></span> <span style="border: 1px solid black; width: 30px; height: 20px; display: inline-block;"></span> <span style="border: 1px solid black; width: 30px; height: 20px; display: inline-block;"></span> </div> </div>																			
<div style="display: flex; justify-content: space-between; font-size: x-small;"> <span>Version 2.0</span> <span>2011-Apr-27</span> </div>																			

## 10.7 Study 4: REMEDY Baseline form

## Appendix 10.7 REMEDY Baseline form

Baseline Questionnaire - Demographics										Page 1	
DataFax #164			Plate #010			Visit #002					
<b>Subject ID</b> <div style="display: flex; justify-content: space-between;"> <div style="width: 30%;"> <div style="border: 1px solid black; width: 20px; height: 20px; display: inline-block;"></div> <div style="border: 1px solid black; width: 20px; height: 20px; display: inline-block;"></div> <div style="border: 1px solid black; width: 20px; height: 20px; display: inline-block;"></div> <div style="border: 1px solid black; width: 20px; height: 20px; display: inline-block;"></div> </div> <div style="width: 30%;"> <div style="border: 1px solid black; width: 20px; height: 20px; display: inline-block;"></div> <div style="border: 1px solid black; width: 20px; height: 20px; display: inline-block;"></div> <div style="border: 1px solid black; width: 20px; height: 20px; display: inline-block;"></div> <div style="border: 1px solid black; width: 20px; height: 20px; display: inline-block;"></div> </div> </div> <div style="display: flex; justify-content: space-between; margin-top: 5px;"> <span>Centre#</span> <span>Subject #</span> </div>										<b>Subject Initials</b> <div style="display: flex; justify-content: space-around;"> <div style="border: 1px solid black; width: 20px; height: 20px; display: inline-block;"></div> <div style="border: 1px solid black; width: 20px; height: 20px; display: inline-block;"></div> <div style="border: 1px solid black; width: 20px; height: 20px; display: inline-block;"></div> </div> <div style="display: flex; justify-content: space-around; margin-top: 5px;"> <span>F</span> <span>M</span> <span>L</span> </div>	
<b>Today's date:</b> <div style="display: flex; justify-content: space-around;"> <div style="border: 1px solid black; width: 20px; height: 20px; display: inline-block;"></div> <div style="border: 1px solid black; width: 20px; height: 20px; display: inline-block;"></div> <div style="border: 1px solid black; width: 20px; height: 20px; display: inline-block;"></div> </div> <div style="display: flex; justify-content: space-around; margin-top: 5px;"> <span>year</span> <span>month</span> <span>day</span> </div>											
<b>Enrolment visit</b>											
<b>1. Date of birth:</b> <div style="display: flex; justify-content: space-around;"> <div style="border: 1px solid black; width: 20px; height: 20px; display: inline-block;"></div> <div style="border: 1px solid black; width: 20px; height: 20px; display: inline-block;"></div> <div style="border: 1px solid black; width: 20px; height: 20px; display: inline-block;"></div> </div> <div style="display: flex; justify-content: space-around; margin-top: 5px;"> <span>year</span> <span>month</span> <span>day</span> </div> <div style="margin-left: 20px;"> <b>OR</b> </div> <div style="margin-left: 20px;"> <b>Age (years)</b> <div style="border: 1px solid black; width: 20px; height: 20px; display: inline-block;"></div> <div style="border: 1px solid black; width: 20px; height: 20px; display: inline-block;"></div> </div> <div style="margin-left: 10px;"> <input type="checkbox"/> accurate  <input type="checkbox"/> estimate         </div>											
<b>2. Sex:</b> <input type="checkbox"/> Male <input type="checkbox"/> Female <div style="margin-left: 20px;"> <b>→ Is this participant pregnant?</b> <input type="checkbox"/> No           <input type="checkbox"/> Yes         </div>											
<b>3. Ethnicity:</b> <div style="border: 1px solid black; width: 20px; height: 20px; display: inline-block;"></div> <div style="border: 1px solid black; width: 20px; height: 20px; display: inline-block;"></div> <div style="margin-left: 10px;">(Please refer to facing page for codes)</div>											
<b>4. Marital status:</b> (check one only) <div style="display: flex; justify-content: space-around; margin-top: 5px;"> <input type="checkbox"/> Never married           <input type="checkbox"/> Currently married           <input type="checkbox"/> Common law/Living with partner           <input type="checkbox"/> Widowed           <input type="checkbox"/> Separated         </div>											
<b>5. What level of formal education have you completed?</b> (check highest level only); (If younger than 7 years of age, check the level of formal education completed by the mother) <div style="display: flex; justify-content: space-around; margin-top: 5px;"> <input type="checkbox"/> None           <input type="checkbox"/> Secondary/High school/Higher secondary           <input type="checkbox"/> College/University           <input type="checkbox"/> Primary           <input type="checkbox"/> Trade school/Vocational school           <input type="checkbox"/> Unknown         </div>											
<b>6. Are you currently employed?</b> <input type="checkbox"/> No <div style="margin-left: 20px;"> <input type="checkbox"/> Yes           <b>→ If yes, what is your average income per month in local currency?</b> <div style="border: 1px solid black; width: 20px; height: 20px; display: inline-block;"></div> <div style="border: 1px solid black; width: 20px; height: 20px; display: inline-block;"></div> <div style="border: 1px solid black; width: 20px; height: 20px; display: inline-block;"></div> <div style="border: 1px solid black; width: 20px; height: 20px; display: inline-block;"></div> <div style="border: 1px solid black; width: 20px; height: 20px; display: inline-block;"></div> <div style="border: 1px solid black; width: 20px; height: 20px; display: inline-block;"></div> </div> <div style="margin-left: 20px;">           What is the local currency? _____           <div style="margin-left: 20px;"> <b>→ US\$</b> <div style="border: 1px solid black; width: 20px; height: 20px; display: inline-block;"></div> <div style="border: 1px solid black; width: 20px; height: 20px; display: inline-block;"></div> <div style="border: 1px solid black; width: 20px; height: 20px; display: inline-block;"></div> </div> <div style="margin-left: 10px;">(for coordinating office only)</div> </div>											

Baseline Questionnaire - Clinical Impressions Page 3

DataFax #164 Plate #012 Visit #002

Subject ID

Centre# Subject #

Subject Initials F M L

11. Approximate date of first referral to hospital for RHD: year month day

12. Clinical Impression: Status at the enrollment visit

a) Valve Lesions

	Absent	Present	Mild (If a clinical impression is INCLUDED by doctor)	Moderate	Severe
i) Mitral Valve					
Stenosis	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Regurgitation	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
ii) Aortic Valve					
Stenosis	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Regurgitation	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
iii) Tricuspid Valve					
Stenosis	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Regurgitation	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
iv) Pulmonary Stenosis					
Stenosis	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Regurgitation	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

b) Clinical evidence of PHT No Yes Unclear ☐ ☐ ☐

c) Evidence of Infective endocarditis ☐ ☐ ☐

d) Congestive heart failure ☐ ☐ ☐

e) Acute rheumatic fever ☐ ☐ ☐



Baseline Questionnaire - ECG/CXR															Page 4	
DataFax #164					Plate #013					Visit #002						
<b>Subject ID</b> <div style="display: flex; justify-content: space-around;"> <div style="border: 1px solid black; width: 30px; height: 20px; display: inline-block;"></div> <div style="border: 1px solid black; width: 30px; height: 20px; display: inline-block;"></div> <div style="border: 1px solid black; width: 30px; height: 20px; display: inline-block;"></div> <div style="border: 1px solid black; width: 30px; height: 20px; display: inline-block;"></div> </div> <div style="display: flex; justify-content: space-around; font-size: small;"> <span>Centre#</span> <span>Subject #</span> </div>																
<b>Subject Initials</b> <div style="display: flex; justify-content: space-around;"> <div style="border: 1px solid black; width: 30px; height: 20px; display: inline-block;"></div> <div style="border: 1px solid black; width: 30px; height: 20px; display: inline-block;"></div> <div style="border: 1px solid black; width: 30px; height: 20px; display: inline-block;"></div> </div> <div style="display: flex; justify-content: space-around; font-size: small;"> <span>F</span> <span>M</span> <span>L</span> </div>																
<b>13. Most recent ECG:</b> a) Was an ECG performed at this visit? <div style="display: flex; justify-content: space-between;"> <div> <input type="checkbox"/> No → Will you be obtaining an ECG for this participant?               </div> <div> <input type="checkbox"/> No → go to section 14.  <input type="checkbox"/> Yes → Complete sections 13.b-e when ECG obtained               </div> </div> <div style="margin-top: 10px;"> <input type="checkbox"/> Yes → Complete section 13.b-e           </div> <div style="display: flex; justify-content: space-between; margin-top: 10px;"> <div>             b) Date:              <div style="display: flex; justify-content: space-around;"> <div style="border: 1px solid black; width: 30px; height: 20px; display: inline-block;"></div> <div style="border: 1px solid black; width: 30px; height: 20px; display: inline-block;"></div> <div style="border: 1px solid black; width: 30px; height: 20px; display: inline-block;"></div> </div> <div style="display: flex; justify-content: space-around; font-size: small;"> <span>year</span> <span>month</span> <span>day</span> </div> </div> <div>             c) Source documentation available:              <input type="checkbox"/> No              <input type="checkbox"/> Yes           </div> </div> <div style="margin-top: 10px;">             d) Rhythm:              <input type="checkbox"/> Sinus              <input type="checkbox"/> Atrial fibrillation              <input type="checkbox"/> Atrial flutter              <input type="checkbox"/> Other Dysrhythmia           </div> <div style="margin-top: 10px;">             e) Other comments (specify): _____           </div>																
<b>14. Most Recent CXR:</b> a) Was a chest x-ray (CXR) performed within last 12 months? <div style="display: flex; justify-content: space-between;"> <div> <input type="checkbox"/> No → Will you be obtaining a CXR for this participant?               </div> <div> <input type="checkbox"/> No → go to section 15.  <input type="checkbox"/> Yes → Complete sections 14.b-g when CXR obtained               </div> </div> <div style="margin-top: 10px;"> <input type="checkbox"/> Yes → Complete section 14.b-g           </div> <div style="display: flex; justify-content: space-between; margin-top: 10px;"> <div>             b) Date:              <div style="display: flex; justify-content: space-around;"> <div style="border: 1px solid black; width: 30px; height: 20px; display: inline-block;"></div> <div style="border: 1px solid black; width: 30px; height: 20px; display: inline-block;"></div> <div style="border: 1px solid black; width: 30px; height: 20px; display: inline-block;"></div> </div> <div style="display: flex; justify-content: space-around; font-size: small;"> <span>year</span> <span>month</span> <span>day</span> </div> </div> <div>             c) CXR report available:              <input type="checkbox"/> No              <input type="checkbox"/> Yes           </div> </div> <div style="margin-top: 10px;"> <div style="display: flex; justify-content: space-between;"> <div>             d) Cardiomegaly              e) Pleural effusion              f) Pulmonary edema           </div> <div style="display: flex; flex-direction: column; align-items: center;"> <div style="display: flex; justify-content: space-around; font-size: small;"> <span>No</span> <span>Yes</span> </div> <div style="display: flex; flex-direction: column; align-items: center;"> <input type="checkbox"/>  <input type="checkbox"/>  <input type="checkbox"/> </div> </div> </div> <div style="margin-top: 10px;">             g) Other comments (Specify): _____           </div> </div>																

Please proceed to complete Page 5

## Baseline Questionnaire - ECHO-1

Page 5

DataFax #164

Plate #014

Visit #002

## Subject ID

Centre#

Subject #

Subject  
Initials
  

F M L

## 15. Echocardiogram

a) Was an Echocardiogram (ECHO) performed at this visit?

☐ No → Has an ECHO been scheduled for this visit?

☐ No → Please Schedule an ECHO now...

☐ Yes → Complete sections 15.b-m when ECHO obtained

☐ Yes → Complete section 15.b-m

Date of most recent Echo report:

year

month

day

Report available:

☐ No

☐ Yes

## Valve Lesions

b) Does the patient have prosthetic valves?

☐ No

☐ Yes

→ If yes, please mark (X) as appropriate:

	Mechanical	Bioprosthesis	Details: (eg type or size)
Mitral	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>
Aortic	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>
Pulmonary	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>
Tricuspid	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>

c) Has the patient had an annuloplasty?

☐ No

☐ Yes → If Yes, please specify:

☐ Mitral

☐ Tricuspid

d) Mitral Valve

Absent

Present

→ Mild

Moderate

Severe (please refer to facing page)

Regurgitation

☐
☐
☐
☐
☐

Stenosis

☐
☐
☐
☐
☐
Please provide gradient information in section i, ii and iii below, if the Mitral valve is **prosthetic or stenotic**:

- i) MVA:       cm<sup>2</sup>  
 ii) End-diastolic gradient:       mmHg  
 iii) Mean gradient:       mmHg

Calcification

☐ No

☐ Yes

Vegetations

☐ No

☐ Yes

Version 2.0

©2011-Mar-02

DataFax #164

Plate #015

Visit #002

## Subject ID

Centre#

Subject #

Subject  
Initials

F M L

## f) Aortic Valve

Absent Present → Mild Moderate Severe (please refer to facing page)

Regurgitation

☐☐☐☐☐

Stenosis

☐☐☐☐☐Please provide gradient information in section i, ii, iii and iv below, if the Aortic valve is **prosthetic or stenotic**:

L i) Jet velocity:

m/s

iii) Mean gradient:

mmHg

ii) Valve area:

cm<sup>2</sup>

iv) Peak gradient:

mmHg

Calcification

☐

No

☐

Yes

Vegetations

☐

No

☐

Yes

## g) Tricuspid Valve

Absent Present → Mild Moderate Severe (please refer to facing page)

Regurgitation

☐☐☐☐☐

Stenosis

☐☐☐☐☐Please provide doppler gradient information below, if the Tricuspid valve is **prosthetic or stenotic**:

L

Doppler gradients (in mmHg): mean

End-diastolic

Calcification

☐

No

☐

Yes

Vegetations

☐

No

☐

Yes

Tricuspid valve annulus

mm

## h) Pulmonary Valve

Absent Present → Mild Moderate Severe (please refer to facing page)

Regurgitation

☐☐☐☐☐

Stenosis

☐☐☐☐☐Please provide doppler gradient information below, if the Pulmonary valve is **prosthetic or stenotic**:

L

Doppler gradients (in mmHg): peak

mean

Calcification

☐

No

☐

Yes

Vegetations

☐

No

☐

Yes

Baseline Questionnaire - ECHO-3

Page 7

DataFax #164 Plate #016 Visit #002

Subject ID

Centre#    Subject #

Subject Initials    F M L

i) Pulmonary hypertension TR gradient:   .   mmHg

TR velocity:   .   m/s

j) Left ventricular dimensions LVIDd   .   mm

LVIDs   .   mm

k) Left ventricular ejection fraction:   .   %

l) Left ventricular shortening fraction:   .   %

m) Left atrium AO:   .   mm

LA:   .   mm

LA:AO ratio:   .

n) Additional echo findings:

Spontaneous echo contrast ☐ No ☐ Yes

Pericardial effusion ☐ No ☐ Yes

Left atrial thrombus ☐ No ☐ Yes

Details: \_\_\_\_\_

Size:    x    mm

Thrombi other than LA ☐ No ☐ Yes

Details: \_\_\_\_\_

Size:    x    mm

o) Further comments: \_\_\_\_\_

Baseline Questionnaire - ECHO-4															Page 8	
DataFax #164					Plate #017					Visit #002						
<b>Subject ID</b> <div style="display: flex; justify-content: space-around;"> <div style="text-align: center;"> <div style="border: 1px solid black; width: 20px; height: 20px; display: inline-block;"></div> <div style="border: 1px solid black; width: 20px; height: 20px; display: inline-block;"></div> <div style="border: 1px solid black; width: 20px; height: 20px; display: inline-block;"></div> </div> <div style="text-align: center;"> <div style="border: 1px solid black; width: 20px; height: 20px; display: inline-block;"></div> <div style="border: 1px solid black; width: 20px; height: 20px; display: inline-block;"></div> <div style="border: 1px solid black; width: 20px; height: 20px; display: inline-block;"></div> <div style="border: 1px solid black; width: 20px; height: 20px; display: inline-block;"></div> </div> </div> <div style="display: flex; justify-content: space-around; margin-top: 5px;"> <span>Centre#</span> <span>Subject #</span> </div>																
												<b>Subject Initials</b> <div style="display: flex; justify-content: space-around;"> <div style="border: 1px solid black; width: 20px; height: 20px; display: inline-block;"></div> <div style="border: 1px solid black; width: 20px; height: 20px; display: inline-block;"></div> <div style="border: 1px solid black; width: 20px; height: 20px; display: inline-block;"></div> </div> <div style="display: flex; justify-content: space-around; margin-top: 5px;"> <span>F</span> <span>M</span> <span>L</span> </div>				
<b>16. Typical Echo features</b>																
<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <u>Significant Morphological features</u> <ul style="list-style-type: none"> <li><input type="checkbox"/> Leaflet thickening</li> <li><input type="checkbox"/> Chordal thickening</li> <li><input type="checkbox"/> Excessive leaflet motion</li> <li><input type="checkbox"/> Restricted leaflet motion</li> <li><input type="checkbox"/> Calcification</li> <li><input type="checkbox"/> Nodules</li> <li><input type="checkbox"/> Vegetations</li> <li><input type="checkbox"/> Hockey stick deformity</li> </ul> </div> <div style="width: 10%; text-align: center;"> <b>AND/OR</b> </div> <div style="width: 45%;"> <u>Significant Regurgitation involving 1 or more valves</u> <ul style="list-style-type: none"> <li><input type="checkbox"/> Seen in more than 1 plane</li> <li><input type="checkbox"/> High velocity doppler &gt; 3m/s</li> <li><input type="checkbox"/> Regurgitation jet length of &gt;1cm OR Multiple jets</li> </ul> </div> </div>																
<b>17. Likelihood of RHD</b> <div style="display: flex; justify-content: flex-end; gap: 20px;"> <input type="checkbox"/> No           <input type="checkbox"/> Yes         </div>																

Please proceed to complete Page 9

## Baseline Questionnaire

Page 9

DataFax #164

Plate #018

Visit #002

## Subject ID

Centre#

Subject #

## Subject Initials

F M L

**Medication:****18. Secondary prophylaxis**

a) Approximate date of commencing secondary prophylaxis:

year

month

day

☐ IMI☐ P.O

b) Currently on secondary prophylaxis:

☐ No (Please proceed to question 19)
☐ Yes → Specify: ☐ Benzathine penicillin  
☐ Oral agents

i) Benzathine penicillin dose

☐ 4wkly☐ 3wkly☐ 2wkly
 No. of injections received in the past year:  
 (According to records/ Physician's estimate)

 % adherence  
 (See facing page for calculation)

%

ii) Oral agents: (mark (x) as appropriate)

☐

Oral penicillin

(specify compound and dosage):

☐

Others

(specify compound and dosage):

 No. of oral prescriptions filled in past year:  
 (According to Physician's estimate)

 % adherence  
 (According to Physician's estimate)

%

Please proceed to complete Page 10





## Baseline Questionnaire

Page 11

DataFax #164

Plate #020

Visit #002

## Subject ID

--	--	--

Centre#

--	--	--	--

Subject #

Subject  
Initials

--	--	--

F M L

21. Does the participant have Poor oro-dental hygiene: ☐ No ☐ Yes  
(including dental caries, gum disease)

Completing question 22 is optional:

22. HIV Status: ☐ Negative ☐ Positive ☐ Unknown ☐ non-disclosure

Please provide details below if information available:

a) Opportunistic infections: ☐ No ☐ Yes → Details: \_\_\_\_\_

b) If HIV positive, WHO Clinical stage I-IV: 

--	--

 Date of WHO staging: 

year	month	day	

c) CD4 count or % at diagnosis: 

--	--	--	--

 Date of diagnosis: 

year	month	day	

  
OR 

--	--

 %

d) Most recent CD4 Count or %: 

--	--	--	--

 Date of CD4 count or %: 

year	month	day	

  
OR 

--	--

 %

e) ARVs: ☐ No ☐ Yes → If yes, please provide Date of commencement: 

year	month	day	

f) Other comments including regime: \_\_\_\_\_  
\_\_\_\_\_

Person Completing  
Report:

Print Last Name

Initial

Date:

2	0				
---	---	--	--	--	--

Version 2.0

2011-Mar-02



**10.8 Study 4: List of participating sites and country**

Country	Investigator	Institution	N, (%)
<b>Egypt</b>	Prof. Azza Abul-Fadl	Faculty of Medicine, Benha University, Cairo	40 (1.2)
	Prof. Sahar Shaker Sheta	Paediatric Cardiology, Cairo University Children's Hospital, Cairo	246 (7.4)
<b>Ethiopia</b>	Prof. Abraham Haileamlak	Department of Paediatrics and Child Health, Jimma University Hospital, Jimma	200 (6.0)
	Dr DejumaYadeta	Department of Internal Medicine, Faculty of Medicine, University of Addis Ababa, Addis Ababa	200 (6.0)
<b>India</b>	Prof. Ganesan Karthikeyan	Department of Cardiology, All India Institute of Medical Sciences, New Delhi, India	293 (8.8)
<b>Kenya</b>	Prof. Stephen Ogendo	Department of Surgery, School of Medicine, College of Health Sciences, University of Nairobi, Nairobi	316 (9.5)
<b>Malawi</b>	Dr Neil Kennedy	Department of Paediatrics and Child Health, College of Medicine, University of Malawi, Blantyre	37 (1.1)
<b>Mozambique</b>	Prof. Albertino Damasceno	Department of Cardiology, Eduardo Mondlane University, Maputo	31 (0.9)
	Dr Ana Olga Mocumbi	Instituto Nacional de Saúde and Eduardo Mondlane University, Maputo	10 (0.3)
<b>Namibia</b>	Dr Chris Hugo-Hamman	Windhoek Central Hospital, Namibia	266 (8.0)
<b>Nigeria</b>	Dr Moshood Adeoye	University College Hospital, Ibadan	9 (0.3)
	Prof. Fidelia Bode-Thomas	Jos University Teaching Hospital, Jos	142 (4.4)
	Dr Okechukwu Ogah	Federal Medical Centre, Abeokuta	12 (0.4)

	Dr Dike Ojji	University of Abuja Teaching Hospital, Abuja	7 (0.2)
	Prof. Mahmoud Sani	Aminu Kano Teaching Hospital, Kano	29 (0.9)
<b>Rwanda</b>	Dr Joseph Mucumbitsi	Paediatric Cardiology Unit, Department of Paediatrics, King Faisal Hospital, Kigali	5 (0.2)
<b>South Africa</b>	Dr. Blanche Cupido	Groote Schuur Hospital, Cape Town	489 (14.6)
	Prof. Phindile Mntla	Department of Cardiology, Dr. George Mukhari Hospital and University of Limpopo (MEDUNSA Campus), Tshwane	9 (0.3)
	Dr Chris Sutton	Mankweng Hospital, Polokwane	57 (1.7)
	Dr Liesl Zühlke	Red Cross War Memorial Children's Hospital, Cape Town	42 (1.3)
<b>Sudan</b>	Prof. Ahmed El-Sayed	Cardiothoracic Surgery Department, AlShaab Teaching Hospital and Alzaiem Alazhari University, Khartoum	159 (4.8)
	Huda H. M. Elhassan	Ahmed Gasim Teaching Hospital, Khartoum	16 (0.5)
<b>Uganda</b>	Dr Charles Mondo	Mulago Hospital and Uganda Heart Institute, Kampala	311 (9.4)
<b>Yemen</b>	Prof. Mohammed Al-Kebsi	Sana'a University, Sana'a	301 (9.0)
<b>Zambia</b>	Dr John Musuku	University Teaching Hospital, Lusaka	116 (3.5)

Appendix 10.9 12 and 24 month Follow-up forms

12 Month Follow-up Visit - Measures										Page 1	
DataFax #164			Plate #030			Visit #003					
<b>Subject ID</b> <div style="display: flex; justify-content: space-between;"> <div style="display: flex; align-items: center;"> <div style="border: 1px solid black; width: 20px; height: 20px; margin-right: 5px;"></div> <div style="border: 1px solid black; width: 20px; height: 20px; margin-right: 5px;"></div> <div style="border: 1px solid black; width: 20px; height: 20px; margin-right: 5px;"></div> </div> <div style="display: flex; align-items: center;"> <div style="border: 1px solid black; width: 20px; height: 20px; margin-right: 5px;"></div> <div style="border: 1px solid black; width: 20px; height: 20px; margin-right: 5px;"></div> <div style="border: 1px solid black; width: 20px; height: 20px; margin-right: 5px;"></div> <div style="border: 1px solid black; width: 20px; height: 20px; margin-right: 5px;"></div> </div> </div> <div style="display: flex; justify-content: space-between; margin-top: 5px;"> <span>Centre#</span> <span>Subject #</span> </div>										<b>Subject Initials</b> <div style="display: flex; align-items: center;"> <div style="border: 1px solid black; width: 20px; height: 20px; margin-right: 5px;"></div> <div style="border: 1px solid black; width: 20px; height: 20px; margin-right: 5px;"></div> <div style="border: 1px solid black; width: 20px; height: 20px; margin-right: 5px;"></div> </div> <div style="display: flex; justify-content: space-around; margin-top: 5px;"> <span>F</span> <span>M</span> <span>L</span> </div>	
<b>Visit date:</b> <div style="display: flex; align-items: center; margin-top: 5px;"> <div style="border: 1px solid black; width: 20px; height: 20px; margin-right: 5px;"></div> <div style="border: 1px solid black; width: 20px; height: 20px; margin-right: 5px;"></div> <div style="border: 1px solid black; width: 20px; height: 20px; margin-right: 5px;"></div> <div style="border: 1px solid black; width: 20px; height: 20px; margin-right: 5px;"></div> <div style="border: 1px solid black; width: 20px; height: 20px; margin-right: 5px;"></div> <div style="border: 1px solid black; width: 20px; height: 20px; margin-right: 5px;"></div> </div> <div style="display: flex; justify-content: space-around; margin-top: 5px;"> <span>year</span> <span>month</span> <span>day</span> </div>											
<b>1. Visit and medication adherence:</b> Did participant complete follow-up clinic visit? <input type="checkbox"/> No → If no, complete the rest of Question 1 <input type="checkbox"/> Yes											
<input type="checkbox"/> Information obtained by telephone visit → Continue to complete the visit form											
<input type="checkbox"/> Information obtained through third party (i.e. family physician, medical records) → Date info obtained from 3rd party: <div style="display: flex; align-items: center; margin-top: 5px;"> <div style="border: 1px solid black; width: 20px; height: 20px; margin-right: 5px;"></div> <div style="border: 1px solid black; width: 20px; height: 20px; margin-right: 5px;"></div> <div style="border: 1px solid black; width: 20px; height: 20px; margin-right: 5px;"></div> </div> <div style="display: flex; justify-content: space-around; margin-top: 5px;"> <span>year</span> <span>month</span> <span>day</span> </div>											
→ <input type="checkbox"/> Family Physician <input type="checkbox"/> Relative or Friend <input type="checkbox"/> Other(specify) _____											
<input type="checkbox"/> Refuses Further Participation → Will participant agree to telephone/mail follow-up? <input type="checkbox"/> Yes → Continue to Follow <div style="text-align: right; margin-right: 50px;">Complete information for this visit and contact Project Office</div> <input type="checkbox"/> No →											
<input type="checkbox"/> Lost → <div style="display: flex; align-items: center; margin-top: 5px;"> <div style="margin-right: 10px;">Number of attempts made to contact the patient</div> <div style="border: 1px solid black; width: 20px; height: 20px; margin-right: 5px;"></div> <div style="margin-left: 10px;">(If less than 4 attempts please attempt contact again)</div> </div>											
→ Was primary contact person/relative contacted? <input type="checkbox"/> Yes <input type="checkbox"/> No → (If no, please do so)											
→ Was primary care physician contacted? <input type="checkbox"/> Yes <input type="checkbox"/> No → (If no, please do so)											
<input type="checkbox"/> Died → Complete and Fax Death Report											
<b>2. Contact Information Update:</b> Has any of the following information changed for this participant since their last visit:											
<div style="display: flex; justify-content: space-between;"> <div style="width: 40%;">         a) Name          b) Hospital #          c) Home Address/phone; Work Phone; Cell Phone          d) Primary or Secondary Contact Person          e) Local Physician OR Clinic       </div> <div style="width: 10%; text-align: center;">         No              Yes      </div> <div style="width: 45%;"> <div style="border-left: 2px solid black; height: 100px; margin-left: 10px;"></div> <div style="margin-left: 10px;">           If "Yes" to any of these, please complete the "contact details report"         </div> </div> </div>											
<b>3. Measurements:</b>											
<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;">         a) Blood Pressure:         <div style="display: flex; align-items: center; margin-top: 5px;"> <div style="border: 1px solid black; width: 20px; height: 20px; margin-right: 5px;"></div> <div style="border: 1px solid black; width: 20px; height: 20px; margin-right: 5px;"></div> <div style="border: 1px solid black; width: 20px; height: 20px; margin-right: 5px;"></div> <div style="margin: 0 5px;">/</div> <div style="border: 1px solid black; width: 20px; height: 20px; margin-right: 5px;"></div> <div style="border: 1px solid black; width: 20px; height: 20px; margin-right: 5px;"></div> <div style="border: 1px solid black; width: 20px; height: 20px; margin-right: 5px;"></div> </div> <div style="margin-left: 5px;">mmHg</div> </div> <div style="width: 45%;">         b) Pulse rate:         <div style="display: flex; align-items: center; margin-top: 5px;"> <div style="border: 1px solid black; width: 20px; height: 20px; margin-right: 5px;"></div> <div style="border: 1px solid black; width: 20px; height: 20px; margin-right: 5px;"></div> <div style="border: 1px solid black; width: 20px; height: 20px; margin-right: 5px;"></div> </div> <div style="margin-left: 5px;">beats/min</div> </div> </div>											
c) Weight: <div style="display: flex; align-items: center; margin-top: 5px;"> <div style="border: 1px solid black; width: 20px; height: 20px; margin-right: 5px;"></div> <div style="border: 1px solid black; width: 20px; height: 20px; margin-right: 5px;"></div> <div style="border: 1px solid black; width: 20px; height: 20px; margin-right: 5px;"></div> <div style="margin: 0 5px;">.</div> <div style="border: 1px solid black; width: 20px; height: 20px; margin-right: 5px;"></div> </div> <div style="margin-left: 5px;">kg</div>											
d) Irregular rhythm: <input type="checkbox"/> No <input type="checkbox"/> Yes											
e) Height: <div style="display: flex; align-items: center; margin-top: 5px;"> <div style="border: 1px solid black; width: 20px; height: 20px; margin-right: 5px;"></div> <div style="border: 1px solid black; width: 20px; height: 20px; margin-right: 5px;"></div> <div style="border: 1px solid black; width: 20px; height: 20px; margin-right: 5px;"></div> <div style="margin: 0 5px;">.</div> <div style="border: 1px solid black; width: 20px; height: 20px; margin-right: 5px;"></div> </div> <div style="margin-left: 5px;">cm</div>											
<div style="display: flex; justify-content: space-between; font-size: small;"> <span>Version 4.3</span> <span>2018-Apr-02</span> </div>											

## 10.9 Study 5: 12 and 24 month outcomes

## Appendix 10.9 REMEDY 12 and 24-month forms

12 Month Follow-up Visit - Outcomes										Page 2																																																																							
DataFax #164		Plate #031		Visit #003																																																																													
<b>Subject ID</b> <div style="display: flex; justify-content: space-around;"> <div style="border: 1px solid black; width: 40px; height: 20px; display: flex; align-items: center; justify-content: center;"> <div style="width: 15px; height: 15px; border: 1px solid black;"></div> <div style="width: 15px; height: 15px; border: 1px solid black;"></div> <div style="width: 10px; height: 15px; border: 1px solid black;"></div> </div> <div style="border: 1px solid black; width: 40px; height: 20px; display: flex; align-items: center; justify-content: center;"> <div style="width: 15px; height: 15px; border: 1px solid black;"></div> <div style="width: 15px; height: 15px; border: 1px solid black;"></div> <div style="width: 10px; height: 15px; border: 1px solid black;"></div> </div> </div> <div style="display: flex; justify-content: space-around; font-size: small;"> <span>Centre#</span> <span>Subject #</span> </div>					<b>Subject Initials</b> <div style="display: flex; align-items: center;"> <div style="border: 1px solid black; width: 20px; height: 20px; display: flex; align-items: center; justify-content: center;"> <div style="width: 10px; height: 10px; border: 1px solid black;"></div> </div> <div style="border: 1px solid black; width: 20px; height: 20px; display: flex; align-items: center; justify-content: center;"> <div style="width: 10px; height: 10px; border: 1px solid black;"></div> </div> <div style="border: 1px solid black; width: 20px; height: 20px; display: flex; align-items: center; justify-content: center;"> <div style="width: 10px; height: 10px; border: 1px solid black;"></div> </div> </div> <div style="display: flex; justify-content: space-around; font-size: x-small; margin-top: 2px;"> <span>F</span> <span>M</span> <span>L</span> </div>																																																																												
<b>4. Status at the current visit:</b> a) Symptoms: (please mark (X) as appropriate) <div style="display: flex; flex-wrap: wrap; margin-top: 5px;"> <div style="width: 33%;"><input type="checkbox"/> Asymptomatic</div> <div style="width: 33%;"><input type="checkbox"/> Chest pain</div> <div style="width: 33%;"><input type="checkbox"/> Routine clinic visit</div> <div style="width: 33%;"><input type="checkbox"/> Dyspnea</div> <div style="width: 33%;"><input type="checkbox"/> Fever</div> <div style="width: 33%;"><input type="checkbox"/> Palpitations</div> <div style="width: 33%;"><input type="checkbox"/> Syncope</div> <div style="width: 33%;"><input type="checkbox"/> Fatigue</div> <div style="width: 33%;"><input type="checkbox"/> Other, Specify: _____</div> </div> b) NYHA class <span style="font-size: small;">➔ (please refer to facing page for codes)</span> <input type="checkbox"/> I <input type="checkbox"/> II <input type="checkbox"/> III <input type="checkbox"/> IV																																																																																	
<b>5. Events:</b> (As taken from doctor's notes and patient's recollection) <table border="1" style="width: 100%; border-collapse: collapse; margin-top: 5px;"> <thead> <tr> <th></th> <th>No</th> <th>Yes</th> <th>Number of Episodes</th> <th>Report#</th> <th>Report#</th> </tr> </thead> <tbody> <tr> <td>a) Congestive Heart Failure</td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><div style="border: 1px solid black; width: 30px; height: 20px; display: flex; align-items: center; justify-content: center;"><div style="width: 15px; height: 15px; border: 1px solid black;"></div></div></td> <td><div style="border: 1px solid black; width: 40px; height: 20px; display: flex; align-items: center; justify-content: center;">1 2</div></td> <td><div style="border: 1px solid black; width: 40px; height: 20px; display: flex; align-items: center; justify-content: center;">1 2</div></td> </tr> <tr> <td>b) Stroke/TIA</td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><div style="border: 1px solid black; width: 30px; height: 20px; display: flex; align-items: center; justify-content: center;"><div style="width: 15px; height: 15px; border: 1px solid black;"></div></div></td> <td><div style="border: 1px solid black; width: 40px; height: 20px; display: flex; align-items: center; justify-content: center;">1 3</div></td> <td><div style="border: 1px solid black; width: 40px; height: 20px; display: flex; align-items: center; justify-content: center;">1 3</div></td> </tr> <tr> <td>c) Hospitalization</td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><div style="border: 1px solid black; width: 30px; height: 20px; display: flex; align-items: center; justify-content: center;"><div style="width: 15px; height: 15px; border: 1px solid black;"></div></div></td> <td><div style="border: 1px solid black; width: 40px; height: 20px; display: flex; align-items: center; justify-content: center;">1 4</div></td> <td><div style="border: 1px solid black; width: 40px; height: 20px; display: flex; align-items: center; justify-content: center;">1 4</div></td> </tr> <tr> <td>d) Major Bleeding</td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><div style="border: 1px solid black; width: 30px; height: 20px; display: flex; align-items: center; justify-content: center;"><div style="width: 15px; height: 15px; border: 1px solid black;"></div></div></td> <td><div style="border: 1px solid black; width: 40px; height: 20px; display: flex; align-items: center; justify-content: center;">1 5</div></td> <td><div style="border: 1px solid black; width: 40px; height: 20px; display: flex; align-items: center; justify-content: center;">1 5</div></td> </tr> <tr> <td>e) Infective endocarditis</td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><div style="border: 1px solid black; width: 30px; height: 20px; display: flex; align-items: center; justify-content: center;"><div style="width: 15px; height: 15px; border: 1px solid black;"></div></div></td> <td><div style="border: 1px solid black; width: 40px; height: 20px; display: flex; align-items: center; justify-content: center;">1 6</div></td> <td><div style="border: 1px solid black; width: 40px; height: 20px; display: flex; align-items: center; justify-content: center;">1 6</div></td> </tr> <tr> <td>f) Prosthetic Valve Thrombosis</td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><div style="border: 1px solid black; width: 30px; height: 20px; display: flex; align-items: center; justify-content: center;"><div style="width: 15px; height: 15px; border: 1px solid black;"></div></div></td> <td><div style="border: 1px solid black; width: 40px; height: 20px; display: flex; align-items: center; justify-content: center;">1 7</div></td> <td><div style="border: 1px solid black; width: 40px; height: 20px; display: flex; align-items: center; justify-content: center;">1 7</div></td> </tr> <tr> <td>g) Acute Rheumatic Fever</td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><div style="border: 1px solid black; width: 30px; height: 20px; display: flex; align-items: center; justify-content: center;"><div style="width: 15px; height: 15px; border: 1px solid black;"></div></div></td> <td><div style="border: 1px solid black; width: 40px; height: 20px; display: flex; align-items: center; justify-content: center;">1 8</div></td> <td><div style="border: 1px solid black; width: 40px; height: 20px; display: flex; align-items: center; justify-content: center;">1 8</div></td> </tr> <tr> <td>h) Valvuloplasty</td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><div style="border: 1px solid black; width: 30px; height: 20px; display: flex; align-items: center; justify-content: center;"><div style="width: 15px; height: 15px; border: 1px solid black;"></div></div></td> <td><div style="border: 1px solid black; width: 40px; height: 20px; display: flex; align-items: center; justify-content: center;">2 0</div></td> <td><div style="border: 1px solid black; width: 40px; height: 20px; display: flex; align-items: center; justify-content: center;">2 0</div></td> </tr> <tr> <td>i) Valve surgery</td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><div style="border: 1px solid black; width: 30px; height: 20px; display: flex; align-items: center; justify-content: center;"><div style="width: 15px; height: 15px; border: 1px solid black;"></div></div></td> <td><div style="border: 1px solid black; width: 40px; height: 20px; display: flex; align-items: center; justify-content: center;">2 1</div></td> <td><div style="border: 1px solid black; width: 40px; height: 20px; display: flex; align-items: center; justify-content: center;">2 1</div></td> </tr> <tr> <td>j) Systemic embolism</td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><div style="border: 1px solid black; width: 30px; height: 20px; display: flex; align-items: center; justify-content: center;"><div style="width: 15px; height: 15px; border: 1px solid black;"></div></div></td> <td><div style="border: 1px solid black; width: 40px; height: 20px; display: flex; align-items: center; justify-content: center;">2 3</div></td> <td><div style="border: 1px solid black; width: 40px; height: 20px; display: flex; align-items: center; justify-content: center;">2 3</div></td> </tr> <tr> <td>k) Atrial Fibrillation / Flutter</td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><div style="border: 1px solid black; width: 30px; height: 20px; display: flex; align-items: center; justify-content: center;"><div style="width: 15px; height: 15px; border: 1px solid black;"></div></div></td> <td><div style="border: 1px solid black; width: 40px; height: 20px; display: flex; align-items: center; justify-content: center;">2 2</div></td> <td><div style="border: 1px solid black; width: 40px; height: 20px; display: flex; align-items: center; justify-content: center;">2 2</div></td> </tr> </tbody> </table>											No	Yes	Number of Episodes	Report#	Report#	a) Congestive Heart Failure	<input type="checkbox"/>	<input type="checkbox"/>	<div style="border: 1px solid black; width: 30px; height: 20px; display: flex; align-items: center; justify-content: center;"><div style="width: 15px; height: 15px; border: 1px solid black;"></div></div>	<div style="border: 1px solid black; width: 40px; height: 20px; display: flex; align-items: center; justify-content: center;">1 2</div>	<div style="border: 1px solid black; width: 40px; height: 20px; display: flex; align-items: center; justify-content: center;">1 2</div>	b) Stroke/TIA	<input type="checkbox"/>	<input type="checkbox"/>	<div style="border: 1px solid black; width: 30px; height: 20px; display: flex; align-items: center; justify-content: center;"><div style="width: 15px; height: 15px; border: 1px solid black;"></div></div>	<div style="border: 1px solid black; width: 40px; height: 20px; display: flex; align-items: center; justify-content: center;">1 3</div>	<div style="border: 1px solid black; width: 40px; height: 20px; display: flex; align-items: center; justify-content: center;">1 3</div>	c) Hospitalization	<input type="checkbox"/>	<input type="checkbox"/>	<div style="border: 1px solid black; width: 30px; height: 20px; display: flex; align-items: center; justify-content: center;"><div style="width: 15px; height: 15px; border: 1px solid black;"></div></div>	<div style="border: 1px solid black; width: 40px; height: 20px; display: flex; align-items: center; justify-content: center;">1 4</div>	<div style="border: 1px solid black; width: 40px; height: 20px; display: flex; align-items: center; justify-content: center;">1 4</div>	d) Major Bleeding	<input type="checkbox"/>	<input type="checkbox"/>	<div style="border: 1px solid black; width: 30px; height: 20px; display: flex; align-items: center; justify-content: center;"><div style="width: 15px; height: 15px; border: 1px solid black;"></div></div>	<div style="border: 1px solid black; width: 40px; height: 20px; display: flex; align-items: center; justify-content: center;">1 5</div>	<div style="border: 1px solid black; width: 40px; height: 20px; display: flex; align-items: center; justify-content: center;">1 5</div>	e) Infective endocarditis	<input type="checkbox"/>	<input type="checkbox"/>	<div style="border: 1px solid black; width: 30px; height: 20px; display: flex; align-items: center; justify-content: center;"><div style="width: 15px; height: 15px; border: 1px solid black;"></div></div>	<div style="border: 1px solid black; width: 40px; height: 20px; display: flex; align-items: center; justify-content: center;">1 6</div>	<div style="border: 1px solid black; width: 40px; height: 20px; display: flex; align-items: center; justify-content: center;">1 6</div>	f) Prosthetic Valve Thrombosis	<input type="checkbox"/>	<input type="checkbox"/>	<div style="border: 1px solid black; width: 30px; height: 20px; display: flex; align-items: center; justify-content: center;"><div style="width: 15px; height: 15px; border: 1px solid black;"></div></div>	<div style="border: 1px solid black; width: 40px; height: 20px; display: flex; align-items: center; justify-content: center;">1 7</div>	<div style="border: 1px solid black; width: 40px; height: 20px; display: flex; align-items: center; justify-content: center;">1 7</div>	g) Acute Rheumatic Fever	<input type="checkbox"/>	<input type="checkbox"/>	<div style="border: 1px solid black; width: 30px; height: 20px; display: flex; align-items: center; justify-content: center;"><div style="width: 15px; height: 15px; border: 1px solid black;"></div></div>	<div style="border: 1px solid black; width: 40px; height: 20px; display: flex; align-items: center; justify-content: center;">1 8</div>	<div style="border: 1px solid black; width: 40px; height: 20px; display: flex; align-items: center; justify-content: center;">1 8</div>	h) Valvuloplasty	<input type="checkbox"/>	<input type="checkbox"/>	<div style="border: 1px solid black; width: 30px; height: 20px; display: flex; align-items: center; justify-content: center;"><div style="width: 15px; height: 15px; border: 1px solid black;"></div></div>	<div style="border: 1px solid black; width: 40px; height: 20px; display: flex; align-items: center; justify-content: center;">2 0</div>	<div style="border: 1px solid black; width: 40px; height: 20px; display: flex; align-items: center; justify-content: center;">2 0</div>	i) Valve surgery	<input type="checkbox"/>	<input type="checkbox"/>	<div style="border: 1px solid black; width: 30px; height: 20px; display: flex; align-items: center; justify-content: center;"><div style="width: 15px; height: 15px; border: 1px solid black;"></div></div>	<div style="border: 1px solid black; width: 40px; height: 20px; display: flex; align-items: center; justify-content: center;">2 1</div>	<div style="border: 1px solid black; width: 40px; height: 20px; display: flex; align-items: center; justify-content: center;">2 1</div>	j) Systemic embolism	<input type="checkbox"/>	<input type="checkbox"/>	<div style="border: 1px solid black; width: 30px; height: 20px; display: flex; align-items: center; justify-content: center;"><div style="width: 15px; height: 15px; border: 1px solid black;"></div></div>	<div style="border: 1px solid black; width: 40px; height: 20px; display: flex; align-items: center; justify-content: center;">2 3</div>	<div style="border: 1px solid black; width: 40px; height: 20px; display: flex; align-items: center; justify-content: center;">2 3</div>	k) Atrial Fibrillation / Flutter	<input type="checkbox"/>	<input type="checkbox"/>	<div style="border: 1px solid black; width: 30px; height: 20px; display: flex; align-items: center; justify-content: center;"><div style="width: 15px; height: 15px; border: 1px solid black;"></div></div>	<div style="border: 1px solid black; width: 40px; height: 20px; display: flex; align-items: center; justify-content: center;">2 2</div>	<div style="border: 1px solid black; width: 40px; height: 20px; display: flex; align-items: center; justify-content: center;">2 2</div>
	No	Yes	Number of Episodes	Report#	Report#																																																																												
a) Congestive Heart Failure	<input type="checkbox"/>	<input type="checkbox"/>	<div style="border: 1px solid black; width: 30px; height: 20px; display: flex; align-items: center; justify-content: center;"><div style="width: 15px; height: 15px; border: 1px solid black;"></div></div>	<div style="border: 1px solid black; width: 40px; height: 20px; display: flex; align-items: center; justify-content: center;">1 2</div>	<div style="border: 1px solid black; width: 40px; height: 20px; display: flex; align-items: center; justify-content: center;">1 2</div>																																																																												
b) Stroke/TIA	<input type="checkbox"/>	<input type="checkbox"/>	<div style="border: 1px solid black; width: 30px; height: 20px; display: flex; align-items: center; justify-content: center;"><div style="width: 15px; height: 15px; border: 1px solid black;"></div></div>	<div style="border: 1px solid black; width: 40px; height: 20px; display: flex; align-items: center; justify-content: center;">1 3</div>	<div style="border: 1px solid black; width: 40px; height: 20px; display: flex; align-items: center; justify-content: center;">1 3</div>																																																																												
c) Hospitalization	<input type="checkbox"/>	<input type="checkbox"/>	<div style="border: 1px solid black; width: 30px; height: 20px; display: flex; align-items: center; justify-content: center;"><div style="width: 15px; height: 15px; border: 1px solid black;"></div></div>	<div style="border: 1px solid black; width: 40px; height: 20px; display: flex; align-items: center; justify-content: center;">1 4</div>	<div style="border: 1px solid black; width: 40px; height: 20px; display: flex; align-items: center; justify-content: center;">1 4</div>																																																																												
d) Major Bleeding	<input type="checkbox"/>	<input type="checkbox"/>	<div style="border: 1px solid black; width: 30px; height: 20px; display: flex; align-items: center; justify-content: center;"><div style="width: 15px; height: 15px; border: 1px solid black;"></div></div>	<div style="border: 1px solid black; width: 40px; height: 20px; display: flex; align-items: center; justify-content: center;">1 5</div>	<div style="border: 1px solid black; width: 40px; height: 20px; display: flex; align-items: center; justify-content: center;">1 5</div>																																																																												
e) Infective endocarditis	<input type="checkbox"/>	<input type="checkbox"/>	<div style="border: 1px solid black; width: 30px; height: 20px; display: flex; align-items: center; justify-content: center;"><div style="width: 15px; height: 15px; border: 1px solid black;"></div></div>	<div style="border: 1px solid black; width: 40px; height: 20px; display: flex; align-items: center; justify-content: center;">1 6</div>	<div style="border: 1px solid black; width: 40px; height: 20px; display: flex; align-items: center; justify-content: center;">1 6</div>																																																																												
f) Prosthetic Valve Thrombosis	<input type="checkbox"/>	<input type="checkbox"/>	<div style="border: 1px solid black; width: 30px; height: 20px; display: flex; align-items: center; justify-content: center;"><div style="width: 15px; height: 15px; border: 1px solid black;"></div></div>	<div style="border: 1px solid black; width: 40px; height: 20px; display: flex; align-items: center; justify-content: center;">1 7</div>	<div style="border: 1px solid black; width: 40px; height: 20px; display: flex; align-items: center; justify-content: center;">1 7</div>																																																																												
g) Acute Rheumatic Fever	<input type="checkbox"/>	<input type="checkbox"/>	<div style="border: 1px solid black; width: 30px; height: 20px; display: flex; align-items: center; justify-content: center;"><div style="width: 15px; height: 15px; border: 1px solid black;"></div></div>	<div style="border: 1px solid black; width: 40px; height: 20px; display: flex; align-items: center; justify-content: center;">1 8</div>	<div style="border: 1px solid black; width: 40px; height: 20px; display: flex; align-items: center; justify-content: center;">1 8</div>																																																																												
h) Valvuloplasty	<input type="checkbox"/>	<input type="checkbox"/>	<div style="border: 1px solid black; width: 30px; height: 20px; display: flex; align-items: center; justify-content: center;"><div style="width: 15px; height: 15px; border: 1px solid black;"></div></div>	<div style="border: 1px solid black; width: 40px; height: 20px; display: flex; align-items: center; justify-content: center;">2 0</div>	<div style="border: 1px solid black; width: 40px; height: 20px; display: flex; align-items: center; justify-content: center;">2 0</div>																																																																												
i) Valve surgery	<input type="checkbox"/>	<input type="checkbox"/>	<div style="border: 1px solid black; width: 30px; height: 20px; display: flex; align-items: center; justify-content: center;"><div style="width: 15px; height: 15px; border: 1px solid black;"></div></div>	<div style="border: 1px solid black; width: 40px; height: 20px; display: flex; align-items: center; justify-content: center;">2 1</div>	<div style="border: 1px solid black; width: 40px; height: 20px; display: flex; align-items: center; justify-content: center;">2 1</div>																																																																												
j) Systemic embolism	<input type="checkbox"/>	<input type="checkbox"/>	<div style="border: 1px solid black; width: 30px; height: 20px; display: flex; align-items: center; justify-content: center;"><div style="width: 15px; height: 15px; border: 1px solid black;"></div></div>	<div style="border: 1px solid black; width: 40px; height: 20px; display: flex; align-items: center; justify-content: center;">2 3</div>	<div style="border: 1px solid black; width: 40px; height: 20px; display: flex; align-items: center; justify-content: center;">2 3</div>																																																																												
k) Atrial Fibrillation / Flutter	<input type="checkbox"/>	<input type="checkbox"/>	<div style="border: 1px solid black; width: 30px; height: 20px; display: flex; align-items: center; justify-content: center;"><div style="width: 15px; height: 15px; border: 1px solid black;"></div></div>	<div style="border: 1px solid black; width: 40px; height: 20px; display: flex; align-items: center; justify-content: center;">2 2</div>	<div style="border: 1px solid black; width: 40px; height: 20px; display: flex; align-items: center; justify-content: center;">2 2</div>																																																																												
<b>6. Pregnancy:</b> (For Women Only) <div style="margin-top: 5px;">             Has this participant become pregnant since her last visit? <input type="checkbox"/> No  <input type="checkbox"/> Yes ➔ Please complete "Pregnancy Report"           </div> <div style="margin-top: 5px; text-align: right;"> <div style="border: 1px solid black; width: 40px; height: 20px; display: flex; align-items: center; justify-content: center;">1 9</div> </div>																																																																																	

12 Month Follow-up Visit - ECG/CXR															Page 3																					
DataFax #164															Plate #013											Visit #003										

**Subject ID**

Centre#			Subject #				

**Subject Initials**

F	M	L

**7. Most recent ECG:**

a) Was an ECG performed at this visit? (ECG is only required if clinically indicated)

☐ No → Will you be obtaining an ECG for this participant? ☐ No → go to section 7.☐ Yes → Complete sections 6.b-e when ECG obtained☐ Yes → Complete section 6.b-eb) Date: 

year			

month		

day	

c) Source documentation available: ☐ No ☐ Yesd) Rhythm: ☐ Sinus ☐ Atrial fibrillation ☐ Atrial flutter ☐ Other Dysrhythmia

e) Other comments (specify): \_\_\_\_\_

**8. Most Recent CXR:**

a) Was a chest x-ray (CXR) performed within last 12 months? (CXR is only required if clinically indicated)

☐ No → Will you be obtaining a CXR for this participant? ☐ No → go to section 8.☐ Yes → Complete sections 7.b-g when CXR obtained☐ Yes → Complete section 7.b-gb) Date: 

year			

month		

day	

c) CXR report available: ☐ No ☐ Yesd) Cardiomegaly: 

No	Yes

e) Pleural effusion: 

No	Yes

f) Pulmonary edema: 

No	Yes

g) Other comments (Specify): \_\_\_\_\_

**Please proceed to complete Page 4**

## 12 Month Follow-up Visit - ECHO-1

Page 4

DataFax #164

Plate #014

Visit #003

## Subject ID

Centre#

Subject #

Subject  
Initials
  

F M L

## 9. Echocardiogram

a) Was an Echocardiogram (ECHO) performed at this visit?

☐ No → Has an ECHO been scheduled for this visit?

☐ No → Please Schedule an ECHO now.

☐ Yes → Complete sections 8, b-m when ECHO obtained

☐ Yes → Complete section 8, b-m

Date of most recent Echo report:

year

month

day

Report available:

☐ No

☐ Yes

## Valve Lesions

b) Does the patient have prosthetic valves?

☐ No

☐ Yes

→ If yes, please mark (X) as appropriate:

	Mechanical	Bioprosthesis	Details: (eg type or size)
Mitral	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>
Aortic	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>
Pulmonary	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>
Tricuspid	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>

c) Has the patient had an annuloplasty?

☐ No

☐ Yes

→ If Yes, please specify:

☐ Mitral

☐ Tricuspid

d) Mitral Valve

Absent

Present

→ Mild

Moderate

Severe (please refer to facing page)

Regurgitation

☐
☐
☐
☐
☐

Stenosis

☐
☐
☐
☐
☐
Please provide gradient information in section i, ii and iii below, if the Mitral valve is **prosthetic or stenotic**:

i) MVA:

   cm<sup>2</sup>

ii) End-diastolic gradient:

    mmHg

iii) Mean gradient:

    mmHg

Calcification

☐ No

☐ Yes

Vegetations

☐ No

☐ Yes

Version 1.1

2013-Apr-02

DataFax #164 Plate #015 Visit #003

Subject ID

Centre#     Subject #

Subject Initials      
F M L

f) Aortic Valve Absent Present → Mild Moderate Severe (please refer to facing page)

Regurgitation	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Stenosis	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Please provide gradient information in section i, ii, iii and iv below, if the Aortic valve is **prosthetic or stenotic**:

→ i) Jet velocity:    m/s iii) Mean gradient:    mmHg

ii) Valve area:    cm<sup>2</sup> iv) Peak gradient:    mmHg

Calcification ☐ No ☐ Yes

Vegetations ☐ No ☐ Yes

g) Tricuspid Valve Absent Present → Mild Moderate Severe (please refer to facing page)

Regurgitation	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Stenosis	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Please provide doppler gradient information below, if the Tricuspid valve is **prosthetic or stenotic**:

→ Doppler gradients (in mmHg): mean    End-diastolic

Calcification ☐ No ☐ Yes

Vegetations ☐ No ☐ Yes

h) Pulmonary Valve Absent Present → Mild Moderate Severe (please refer to facing page)

Regurgitation	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Stenosis	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Please provide doppler gradient information below, if the Pulmonary valve is **prosthetic or stenotic**:

→ Doppler gradients (in mmHg): peak    mean

Calcification ☐ No ☐ Yes

Vegetations ☐ No ☐ Yes

12 Month Follow-up Visit - ECHO-3

Page 6

DataFax #164

Plate #016

Visit #003

Subject ID

Centre#

Subject #

Subject  
Initials

F M L

i) Pulmonary hypertension

TR gradient:

.

mmHg

TR velocity:

.

m/s

j) Left ventricular dimensions

LVIDd

.

mm

LVIDs

.

mm

k) Left ventricular ejection fraction:

.

%

l) Left ventricular shortening fraction:

.

%

m) Left atrium

AO:

.

mm

LA:

.

mm

LA:AO ratio:

.

n) Additional echo findings:

Spontaneous echo contrast

☐ No ☐ Yes

Pericardial effusion

☐ No ☐ Yes

Left atrial thrombus

☐ No ☐ Yes

Details: \_\_\_\_\_

Size:    x    mm

Thrombi other than LA

☐ No ☐ Yes

Details: \_\_\_\_\_

Size:    x    mm

o) Further comments: \_\_\_\_\_

Version 1.1

2013-Apr-02



12 Month Follow-up Visit - Medication-1															Page 7
DataFax #164	Plate #032	Visit #003													

Subject ID

Centre#

Subject #

Subject  
Initials
  

F M L

**Medication:****10. Secondary prophylaxis**

a) Has the participant ever used secondary prophylaxis:

☐ No (Please proceed to question 6)
☐ Yes → Specify: ☐ Benzathine penicillin  
☐ Oral agents

→ Specify: ☐ Currently on secondary prophylaxis  
☐ Past use of secondary prophylaxis
b) Approximate date of commencing  
secondary prophylaxis:
   

year

month

day

 
☐ IMI

☐ P.O.

i) Benzathine penicillin dose

→ ☐ 4wkly☐ 3wkly☐ 2wkly
No. of injections received in the past year:  
(According to records/ Physician's estimate)

% adherence  
( See facing page for calculation)

%

ii) Oral agents: (mark (x) as appropriate)

☐ Oral penicillin  
(specify compound  
and dosage):

☐ Others  
(specify compound  
and dosage):

No. of oral prescriptions filled in past year:  
(According to Physician's estimate)

% adherence  
(According to Physician's estimate)

%

Please proceed to complete Page 8



DataFax #164

Plate #019

Visit #003

## Subject ID

Centre#

Subject #

Subject  
Initials
  

F M L

## 11. Oral anticoagulation

a) Is patient in sinus rhythm? ☐ No  
☐ Yes

ECG available ☐ No ☐ Yes

b) Has oral anticoagulation been prescribed? ☐ No  
☐ Yes (If yes, please provide details below)

☐ Warfarin → i) How many measurements of INR have been performed in the last 6 months?

☐ None ☐ 1-3 ☐ 4-6 ☐ >6

ii) Is patient aware of what his/her INR should be?

☐ No

☐ Yes → if yes, what is the target INR?  .   to  .    
 (According to patient)

iii) Last three INR values:

1-  .   → Dated:        
year month day

2-  .   → Dated:        
year month day

3-  .   → Dated:        
year month day

☐ Acenocoumalone

☐ Aspirin

☐ Others specify: \_\_\_\_\_

## 12. Other medication: (Please mark (X) as appropriate)

	No	Yes
a) Beta-adrenergic blockers	<input type="checkbox"/>	<input type="checkbox"/>
b) Calcium channel blockers	<input type="checkbox"/>	<input type="checkbox"/>
c) Diuretics	<input type="checkbox"/>	<input type="checkbox"/>
d) ACE inhibitors	<input type="checkbox"/>	<input type="checkbox"/>
e) Antiarrhythmics	<input type="checkbox"/>	<input type="checkbox"/>
f) Digoxin	<input type="checkbox"/>	<input type="checkbox"/>
g) Contraceptives	<input type="checkbox"/>	<input type="checkbox"/> Specify: _____
h) Others	<input type="checkbox"/>	<input type="checkbox"/> Specify: _____



## 10.10 Study 4 and 5 : REMEDY Manual of operations

Awareness ♦ Surveillance ♦ Advocacy ♦ Prevention

**A.S.A.P.**

Rheumatic Fever &  
Rheumatic Heart Disease

### GLOBAL RHEUMATIC HEART DISEASE REGISTRY

# ***REMEDY***

## MANUAL OF OPERATIONS

**VERSION 1.3**

**SEPTEMBER 2011**

**Prepared by**

**Dr Liesl Zühlke**

**For the REMEDY Operations Committee**



## TABLE OF CONTENTS

<b>1. GLOSSARY .....</b>	<b>4</b>
<b>2. STUDY OVERVIEW .....</b>	<b>5</b>
<b>3. PATIENT VISIT SCHEDULE .....</b>	<b>7</b>
<b>4. PATIENT ELIGIBILITY .....</b>	<b>8</b>
4.1 inclusion and exclusion criteria .....	8
4.2 Informed Consent .....	8
4.3 Patient Confidentiality .....	9
4.4 Centre Numbers as at 1 August 2011 .....	9
<b>5. REGISTRATION FORM: .....</b>	<b>11</b>
<b>6. BASELINE FORM: .....</b>	<b>13</b>
6.1 THE BASELINE FORM: .....	13
6.2 Ethnicity codes: .....	13
6.3 Occupation codes: .....	14
6.4 Instructions for Physical Measurements Q8 .....	15
6.5 Presenting features Q 9-12 .....	16
6.6 ECG/CXR Q13-14 .....	20
6.6 ECHOCARDIOGRAM Q15-16 .....	20
6.7 Medication Q18-20 .....	30
6.8 HIV optional questions Q21 .....	31
<b>7. FOLLOW-UP FORM .....</b>	<b>34</b>
<b>8. EVENT DEFINITIONS .....</b>	<b>35</b>
<b>9. EVENT FORMS .....</b>	<b>38</b>
9.1 REPORT NO 12 CONGESTIVE Heart failure. ....	38
9.2 REPORT NO 13 STROKE/TIA .....	38
9.3 REPORT 14 HOSPITALISATION .....	38
9.4 REPORT NO 15 MAJOR BLEEDING .....	38
9.5 REPORT NO 16 INFECTIVE ENDOCARDITIS.....	39
9.6 REPORT 17 PROSTHETIC VALVE THROMBOSIS .....	39
9.7 REPORT 18 ACUTE RHEUMATIC FEVER .....	39
9.8 REPORT NO 20 VALVULOPLASTY .....	40

9.9 REPORT NO 21 VALVE SURGERY .....	41
9.10 REPORT NO 23 SYSTEMIC EMBOLISM .....	41
9.11 REPORT NO 22 ATRIAL FIB/FLUTTER .....	42
9.12 REPORT NO 19 PREGNANCY .....	42
9.13 DEATH .....	42
9.14 FINAL POINTS REGARDING ALL CRFS .....	42
<b>10. STUDY OUTCOME EVENTS .....</b>	<b>43</b>
<b>11. STUDY ORGANISATION AND RESPONSIBILITIES .....</b>	<b>44</b>
11.1 ORGANISATION AND GOVERNANCE .....	44
11.2 PUBLICATION POLICY .....	45
11.3 AUTHORSHIP GUIDELINES .....	45
11.4 SUB-STUDIES .....	46
11.5 MEMORANDUM OF AGREEMENT .....	46
11.6 PROJECT COORDINATING OFFICE: .....	46
11.7 INVESTIGATING SITES .....	47
11.8 MAINTENANCE OF RECORDS .....	47
11.9 COMMUNICATION .....	48
<b>12. REFERENCES .....</b>	<b>49</b>
<b>13. Appendices .....</b>	<b>51</b>

1. GLOSSARY	
<b>RHD</b>	<b>Rheumatic Heart Disease</b>
<b>CRF</b>	Case Report Form
<b>ARF</b>	Acute Rheumatic Fever
<b>GCP</b>	Good Clinical Practice
<b>MOP</b>	Manual of Operations
<b>SOP</b>	Standard Operating Procedures
<b>PCO</b>	Project Coordinating Office
<b>PI</b>	Principal Investigator
<b>ERF</b>	Event Record Form

2. STUDY OVERVIEW	
<b>TITLE</b>	THE GLOBAL REGISTRY FOR RHEUMATIC HEART DISEASE-REMEDY (RHEUMATIC HEART DISEASE REGISTRY)
<b>STUDY SIZE</b>	3000 PATIENTS FROM AFRICA, INDIA AND OTHER LOW AND MIDDLE – INOMCE COUNTRIES
<b>STUDY DESIGN</b>	INTERNATIONAL MULTI-CENTRE PROSPECTIVE COHORT DESIGN
<b>PRIMARY OBJECTIVE</b>	<p>TO ASSESS THE MORBIDITY AND MORTALITY OF PATIENTS DIAGNOSED AND TREATED FOR RHEUMATIC FEVER AND RHEUMATIC HEART DISEASE. IN PARTICULAR TO:</p> <ul style="list-style-type: none"> <li>• OUTLINE THE CLINICAL AND DEMOGRAPHIC PROFILES OF PATIENTS WITH RHD IN LOW AND MIDDLE INCOME COUNTRIES</li> <li>• DETERMINE THE CONTEMPORARY TREATMENT OF PATIENTS DIAGNOSED WITH RHEUMATIC HEART DISEASE</li> <li>• DOCUMENT CLINICAL OUTCOMES IN THIS POPULATION</li> </ul>
<b>INCLUSION CRITERIA</b>	<p>1. DIAGNOSIS OF RHEUMATIC FEVER AND/OR RHEUMATIC HEART DISEASE WITH ESTABLISHED VALVE DISEASE.</p> <p>2. AVAILABILITY OF FIXED ADDRESS AND CONTACTABLE RELATIVES</p> <p>3. WILLINGNESS TO PARTICIPATE FOR THE FULL DURATION OF THE TRIAL (24 MONTHS)</p>
<b>EXCLUSION CRITERIA</b>	<p>1. EVIDENCE OF VALVE DISEASE BEING CAUSED BY A DISEASE PROCESS OTHER THAN RHD</p> <p>2. INABILITY TO PROVIDE INFORMED CONSENT</p>



<b>PROJECT COORDINATING OFFICE: AFRICA (PCO)</b>	<p>Dr Liesl Zühlke Department of Medicine, J 46.47 Old Main Building, Groote Schuur Hospital University of Cape Town, Observatory 7925 Telephone: +27-21-4047676; Fax: +27-21-4472765 Email Addresses:  liesl.zuhlke@uct.ac.za</p>
<b>COORDINATING OFFICE: INDIA (PCO)</b>	<p>DR GANESAN KARTHIKAYAN ALL INDIA INSTITUTE OF MEDICAL SCIENCES NEW DELHI, INDIA PHONE: +91-11-26593322 MOBILE: +91-9871074832 FAX: +91-11-26588641</p>
<b>POPULATION HEALTH RESEARCH INSTITUTE (PHRI)</b>	<p>PHRI, HAMILTON GENERAL HOSPITAL, 237 BARTON STREET EAST MAC CLINIC, 2<sup>ND</sup> FLOOR ROOM 252 HAMILTON, ONTARIO L8L 2X2 CANADA TEL. +905-527-4322; FAX: +905-521-1166</p>

3. PATIENT VISIT SCHEDULE

CLINICAL VISIT	1					2					3
VISIT NUMBER	1					2					3
DATE	0					12 MONTHS					24 MONTHS
ELIGIBILITY /-CONSENT	X										
INFORMED CONSENT	X										
REGISTRATION AND BASELINE CRF	X										
FOLLOW-UP FORM						X					X
MEDICAL HISTORY/PHYSICAL EXAM	X	AS PER STANDARD OF CARE				X	AS PER STANDARD OF CARE				X
ECG /-ECHO (AGREED MINIMUM)	X	AS PER STANDARD OF CARE				X	AS PER STANDARD OF CARE				X
ADVERSE EVENT						X					X

Section Break (Next Page)

COMPLETE EVENT FORMS FOR EACH EVENT OCCURRING IN THE PRECEDING YEAR, FROM THE TIME OF ENROLLMENT INTO THE STUDY UP TO AND INCLUDING THE 12-MONTH FOLLOW-UP DATE

COMPLETE EVENT FORMS FOR EACH EVENT OCCURRING IN THE PRECEDING YEAR, FROM THE TIME IMMEDIATELY FOLLOWING THE 12-MONTH VISIT AND UP TO AND INCLUDING THE 24-MONTH FOLLOW-UP DATE

#### 4. PATIENT ELIGIBILITY

**Please maintain a SCREENING LOG of all patients screening for enrolment into Registry with**

##### 4.1 inclusion and exclusion criteria

###### I. Inclusion Criteria [ALL criteria must be present for eligibility to be confirmed]

- Diagnosis of rheumatic fever and/or rheumatic heart disease
- Availability of reliable address and contactable relatives
- Willingness to participate for the full duration of the trial (24 months)

###### II. Exclusion Criteria [none of the criteria must apply for the patient to be eligible]

- Evidence of valve disease being caused by a disease process other than RHD
- Inability to provide informed consent/assent

##### 4.2 Informed Consent

###### **Written Informed consent must be obtained prior to enrolling patients in the study.**

If the patient or person providing the informed consent cannot sign the Informed Consent Form, a thumbprint will suffice.

For future reference, please record in the patient's file:

- The date and time of consent.
- The name of the person obtaining consent.
- The informed consent form.

A template *Informed Consent Form* is included in appendices. This should be adapted and translated for use in each site. A copy of the consent form must be provided to the participant.

##### 4.3 Patient Confidentiality

All patients will be identified by a unique number assigned at enrolment. The number consists currently of a combination of the center number plus the order in which the patient was enrolled.

For example: A patient at center 300 (Groote Schuur Hospital), who was the 4th patient enrolled, will be identified by Patient Identification Number 300-04.

All Case Report Forms and all other study documentation, including source documents and correspondence regarding the patient, must document the center and subject number. Please ensure this number is placed on ALL documents. Patient confidentiality must be upheld in all study documentation. The registration form with contact details must be kept separately from the study documentation to maintain confidentiality as regards data.

#### 4.4. Centre Numbers as at 1 August 2011

100	India: Dr Karthikeyan
101	India: Dr Satheesh
200	Egypt: Dr Sheta
201	Egypt: Dr Azza
210	Ethiopia: Dr Haimeamlak
220	Mozambique: Dr Mocumbi
230	Nigeria: Dr Bode-Thomas
231	Nigeria: Dr Sani
232	Nigeria: Dr Ogah
240	Rwanda: Dr Mucumbitsi
250	Sudan: Dr Sayed
260	Uganda: Dr Mondo
270	Kenya: Dr Yonga

## Appendices

280	Namibia: Dr Hugo-Hamman
290	Yemen: Dr Al-Kebsi
300	South Africa: Dr Mayosi
301	South Africa: Dr Zühlke
302	South Africa: Dr Sutton

## 5. REGISTRATION FORM:

### To complete the registration form:

- Ensure that the participant has signed the consent form.
- Ensure that the participant meets all of the inclusion criteria.
- Ensure that all exclusion criteria are assessed and none apply.
- Confirm that participant meets the eligibility criteria
- Please complete Centre and subject number on each page.
- Please complete subject's initials on every page
- Please answer each question by marking an X in one box on each line OR writing numbers in the spaces provided OR writing neatly and legibly on the lines provided.

### General issues:

- This form is kept separately from Data CRF's and should be filed together with the signed informed consent form.
- The participant's subcategory ID is based on recruiting ward and can be completed if centres are interested in doing sub-analyses according to recruiting wards. Subcategory ID: This refers to a center specific subcategory e.g. Groote Schuur ward: G17, outpatient: E17

### To complete the contact section, please record patient information including:

- Name, initials, home address and phone number(s) of the patient. Include the GPS coordinates if available and hospital number.
- Contact information of at least two contacts including family members, friends or neighbours.
- The contact information of the local clinic.

### General Instructions:

- When completing forms please **use black pen only**. Never use pencil or red pen.
- **If it is necessary to make a correction, please draw a single line through the incorrect value and write the correct value nearby. Please initial and date each correction.** Never use Liquid Paper/Tippex/correction fluid.

- For questions where a number is required for a response and there is more than one box provided, please fill the boxes from right to left and zero fill all empty boxes. For example, a response of 14 cigarettes smoked per day would be recorded as below.

0	1	4
---	---	---

- **Case ID:** These are assigned at enrollment and should be documented and recorded on every page of every subsequent form.
- **Case Initials:** Include an initial for the subject's first, second/middle, and surname. If the subject has no second/middle name, please draw a straight line through the middle box, as demonstrated below.

M	-	L
---	---	---

**Note** - The Case Initials **MUST** be entered at the top of **each** page of every questionnaire. This is critical to data quality. Each page is a separate, unique source of data. Without the identifying pieces of information at the top of every page it is impossible to know to whom the data belongs.

## 6. BASELINE FORM:

### 6.1 THE BASELINE FORM:

- Ensure that all the demographic details are completed and ethnicity and occupation is completed using the codes referred to in 6.2 and 6.3.
- Please enter the date in the format: yyyy-mm-dd
- Please complete subject's initials on every page
- Please answer each question by marking an X in one box on each line OR writing numbers in the spaces provided OR writing neatly and legibly on the lines provided.

### 6.2 ETHNICITY CODES:

**Ethnicity Codes**

- 01 - South Asian (India, Sri Lanka, Pakistan, Bangladesh)
- 02 - Chinese (China, Hong Kong, Taiwan)
- 03 - Japanese
- 04 - Malays
- 05 - Other Asian (Korea, Malaysia, Papua New Guinea, Thailand, Philippines, Indonesia, Nepal, Vietnam, Cambodia, Laos, Myanmar/Burma, Bhutan, Singapore)
- 06 - Persian
- 07 - Arab
- 08 - Black African
- 09 - Coloured African (Subsaharan African only)
- 10 - European
- 11 - Native North/South American or Australian Aborigine
- 12 - Latin American (Latino)
- 13 - Bantu/Semi Bantu
- 14 - Hemitic/Semi Hemitic
- 15 - Nilotic/Hausa
- 16 - Pygmie
- 17 - Swahili
- 18 - Other (any other ethnoracial group not listed above)      (Your own) Listing: \_\_\_\_\_

**6.3 OCCUPATION CODES:**



## **11. Occupation**

### **Group 1: Legislators, senior officials and managers**

Legislators and senior officials  
Corporate managers  
General managers  
Businessman

### **Group 2: Professionals**

Physical, mathematical and engineering science professionals  
Life science and health professionals  
Teaching professionals  
Other professionals

### **Group 3: Technicians and associate professionals**

Physical, mathematical and engineering-  
science associate professionals/technicians  
Life science and health associate professionals/technicians  
Teaching associate professionals/technicians  
Other associate professionals/technicians

### **Group 4: Clerks**

Clerks  
Customer service clerks

### **Group 5: Service workers and shop and market sales workers**

Personal and protective services workers  
Models, salespersons and demonstrators

### **Group 6: Skilled agricultural and fishery workers**

Market-oriented skilled agricultural and fishery workers  
Subsistence agricultural and fishery workers

### **Group 7: Craft and related trade workers**

Extraction and building trade workers  
Metal, machinery and related trades workers  
Precision, handicraft, printing and  
related trades workers  
Other craft and related trades workers

### **Group 8: Plant and machine operators and assemblers**

Stationary plant and related operators  
Machine operators and assemblers  
Drivers and mobile plant operators

### **Group 9: Elementary occupations**

Sales and services elementary occupations  
Agricultural, fishery and related labourers  
Labourers in mining, construction,  
manufacturing and transport

### **Group 10: Armed forces**

Armed forces

### **Group 11: Homemaker**

Housewife/Househusband :A woman/man  
who manages her own household as his/her  
main occupation not merely an unemployed  
person. Need not necessarily be married.

### **Group 12: Student**

Anyone engaged in school / college / tertiary  
level activity

## 6.4 INSTRUCTIONS FOR PHYSICAL MEASUREMENTS Q8

### (Record measurements on Page 1 of Baseline CRF)

Test	Description
<b>Blood Pressure</b>	<p>Use a standard (mercury) sphygmomanometer. Systolic pressure is determined by the first heard sound (Korotkoff phase I). Diastolic pressure is recorded at the level when the sound just disappears (Korotkoff phase V).</p> <p>Ensure adequate cuff size. Bladder should encircle and cover 2/3 of length of arm with the bladder over the brachial artery. Its lower border should be 1 inch (2-3 cm) above the antecubital space. Deflate the bladder slowly. Take a reading on the right arm, and record exact values.</p>
<b>Height</b>	<p>Standing height is measured with the subject in bare feet, back square against the wall and eyes looking straight ahead. A set square resting on the scalp and a tape measurement* from the wall is used to measure height to the nearest 0.5 cm.</p>
<b>Weight</b>	<p>Weight is measured using a platform scale, to the nearest 100 grams. The scales must be standardised to 0 before each use.</p>
<b>Pulse Rate</b>	<p>Measure pulse using the radial artery, felt at the wrist, on the right arm. Count the number of heartbeats during 10 seconds and multiply by 6.</p>

## 6.5 PRESENTING FEATURES Q 9-12

- This section refers to status at enrollment visit. Patients who have come for a routine clinic visit and are asymptomatic may have more than one box checked. Those who are asymptomatic but have come outside of normal clinic appointment times should only have asymptomatic checked.

- NYHA classification:<sup>1</sup>

Class	Patient Symptoms
Class I (Mild)	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnoea (shortness of breath).
Class II (Mild)	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnoea.
Class III (Moderate)	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnoea.
Class IV (Severe)	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

- Past medical History should be taken from hospital records, notes and patients' own recollection. Please retain any source documentation if possible (e.g. CT scan, operation report, hospital discharge records.) The definitions below are given as guides only.

Clinical Impression:

- No clear guidelines exist regarding the clinically grading of valvular disease. However if treating physician has documented a clinical impression regarding the severity of the valvular disease, please indicate this on the form.

Clinical evidence of pulmonary hypertension <sup>2</sup>

The starred signs are the most important and minimum requirement for making the clinical diagnosis of pulmonary hypertension.

<i>Symptoms</i>	<i>Signs</i>
Fatigue	<b>Prominent right ventricular impulse*</b>
Syncope	<b>Accentuated pulmonic valve component (P2)*</b>
Dyspnoea on exertion	Jugular vein distention
Angina chest pain	Right-sided third heart sound (S3)
Hemoptysis	Tricuspid insufficiency murmur

Raynaud's phenomenon

Hepatomegaly and Peripheral edema

Infective endocarditis<sup>3, 4</sup> – should be diagnosed using the modified Duke's criteria. A minor criterion or five minor criteria. Major criteria include:

### Clinical signs of infective endocarditis

#### **Major Criteria:**

Positive blood culture with typical IE microorganism, defined as one of the following: Typical microorganism consistent with IE from 2 separate blood cultures, as noted below:

- Viridans-group streptococci, or *S. bovis* including nutritional variant strains, or HACEK group, or *S. aureus*, or Community-acquired enterococci, in the absence of a primary focus

Microorganisms consistent with IE from persistently positive blood cultures defined as:

- Two positive cultures of blood samples drawn >12 hours apart, or All of 3 or a majority of 4 separate cultures of blood (with first and last sample drawn 1 hour apart) or *Coxiella burnetii* detected by at least one positive blood culture or antiphase I IgG antibody titer >1:800

Evidence of endocardial involvement with positive echocardiogram defined as:

- Oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant jets, or on implanted material in the absence of an alternative anatomic explanation, or Abscess, or New partial dehiscence of prosthetic valve or new valvular regurgitation (worsening or changing of preexisting murmur not sufficient)

#### **Minor Criteria:**

- Predisposition, predisposing heart condition
- Fever, temperature >38C
- Vascular phenomena, major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages and Janeway lesions.
- Immunologic phenomena: Osler's nodes, Roth's spots and rheumatoid factor

- Congestive Heart Failure<sup>5</sup>

FRAMINGHAM CRITERIA	
By the Framingham criteria, diagnosis of congestive heart failure (heart failure with impaired pumping capability) requires the simultaneous presence of at least 2 of the following major criteria or 1 major criterion in conjunction with 2 of the following minor criteria:	
<p>Major criteria:</p> <ul style="list-style-type: none"> <li>• Cardiomegaly on chest radiography</li> <li>• S3 gallop (a third heart sound)</li> <li>• Acute pulmonary edema</li> <li>• Paroxysmal nocturnal dispend</li> <li>• Crackles on lung auscultation</li> <li>• Central venous pressure of more than 16 cm H2O at the right atrium</li> <li>• Jugular vein distension</li> <li>• Positive abdominojugular test</li> <li>• Weight loss of more than 4.5 kg in 5 days in response to treatment (sometimes classified as a minor criterion[34])</li> </ul> <p>Minor criteria:</p> <ul style="list-style-type: none"> <li>• Tachycardia of more than 120 beats per minute</li> <li>• Nocturnal cough</li> <li>• Dyspnoea on ordinary exertion</li> <li>• Pleural effusion</li> <li>• Decrease in vital capacity by one third from maximum recorded</li> <li>• Hepatomegaly</li> <li>• Bilateral ankle edema</li> </ul>	
Minor criteria are acceptable only if they cannot be attributed to another medical condition such as pulmonary hypertension, chronic lung disease, cirrhosis, ascites, or the nephrotic syndrome. The Framingham Heart Study criteria are 100% sensitive and 78% specific for identifying persons with definite congestive heart failure.	

Most recent ECG and CXR: In order for participants not to incur additional costs, these DO NOT need to be repeated at the time of enrollment unless clinically indicated. If clinically relevant,

copies of ECG's and CXR reports should be filed at the site office. These do not need to be sent through to the co-coordinating office.

## 6.6 ECHOCARDIOGRAM

Q15-16

Regular echocardiograms to demonstrate the natural history of the valve lesions is a hallmark of this study. It is thus essential that each participant has at least 2 echoes within a 24 month period. **If echocardiograms are not able to be performed at the time of enrollment, these need to be rescheduled within 3 months of enrollment** in order for the participant to be registered on the database. Unless these are clinically indicated, it is assumed that the sites will cover the costs, if any, of these echoes as part of the study and patients will not have to incur additional costs.

<b>Mitral Valve</b>	<b>Mild Mitral Stenosis</b>	<b>Moderate Mitral Stenosis</b>	<b>Severe Mitral Stenosis</b>
<b>Pressure Half Time</b>	90 to 150 ms	150 to 219 ms	> 220 ms
<b>Mitral Valve area</b>	1.5 to 2.5 cm <sup>2</sup>	1.0 to 1.5 cm <sup>2</sup>	<1.0 cm <sup>2</sup>
<b>End-diastolic pressure gradient</b>	2 to 6mmHg	6 to 10 mm Hg	>10 mm Hg
<b>Mean Pressure gradient</b>	< 5 mmHg	6 to 10 mm Hg	> 10 mm Hg
<b>Pulmonary artery systolic pressure (mmHg)</b>	Less than 30	30-50	>50

<b>Mitral Valve</b>	<b>Mild Mitral Regurgitation</b>	<b>Moderate Mitral Regurgitation</b>	<b>Severe Mitral Regurgitation</b>
<b>CW Doppler signal/jet area</b>	Complete mitral regurgitation envelope as recorded by CW Doppler  Small, central jet (<20% of LA area)	Strong complete MR spectral envelope by CW Doppler	Strong complete mitral regurgitation signal with the gray scale of mitral regurgitation darker than mitral inflow as visualised by CW Doppler
<b>Left atrium and left ventricular enlargement</b>	minimal	Moderate to severe left atrial and left ventricular enlargement	Moderate to severe left atrial and left ventricular enlargement
<b>Doppler vena contracta width (cm)</b>	Less than 0.3	0.3-0.69	> than or equal to 0.7
<b>Regurgitation fraction</b>	<20%	20 to 30%	> 40%, wall-impinging jet of any size, swirling in LA  Regurgitant jet area / left atrial area ratio > 40%
<b>Additional notes:</b>			

#### Mitral Valve – Mitral Valve – Assess by Mean Gradient and Valve Area

Mean Diastolic gradient: Using continuous wave Doppler from the apical window (to allow parallel alignment of u/s beam and mitral inflow). Mean gradient is recorded by tracing the Doppler of the mitral inflow. NB. Mean gradient is not the best marker as it is dependent on mitral valve area, and multiple other factors so needs to be used in conjunction with mitral valve planimetry.

Mitral Valve Planimetry: MVP has the best correlation with anatomical valve areas. MVP is obtained in mid-diastole from the parasternal short-axis view by direct tracing of the mitral orifice, including opened commissures, if applicable. Measurements are made at the level of the leaflet tips, and perpendicular to the mitral orifice.

#### Mitral Valve – Assess by Color Doppler and Vena Contracta

Evaluation of MV severity should integrate multiple parameters to minimise the effects of technical or measurement errors inherent to each method.

Color Doppler: Presence or absence of mitral regurgitation is obtained from the parasternal long-axis view. Regurgitant jet area will be considered with a Nyquist limit between 5060cm/sec and a color gain setting that just eliminates random color speckle from non-moving regions.

Vena Contracta: The vena contracta is imaged in high resolution, zoom views for the largest obtainable proximal jet size for measurements. Parasternal long-axis imaging is used in order to obtain measurements perpendicular to the mitral valve commissure line. The width of the neck or narrowest portion of the jet will then be measured.



<b>Aortic Valve</b>	<b>Mild Aortic Stenosis</b>	<b>Moderate Aortic Stenosis</b>	<b>Severe Aortic Stenosis</b>
<b>Jet velocity (m/s)</b>	Less than 3.0	3.0-4.0	>4.0
<b>Mean gradient (mmHg)</b>	Less than 25	25-40	>40
<b>Valve area (cm<sup>2</sup>)</b>	Greater than 1.5	1.0-1.5	Less than 1.0
<b>Valve area indexed (cm<sup>2</sup>/m<sup>2</sup>)</b>			<0.6

	<b>Mild Aortic Regurgitation</b>	<b>Moderate Aortic Regurgitation</b>	<b>Severe Aortic Regurgitation</b>
<b>CW Doppler jet width</b>	Central jet, width less than 25% of LVOT	Intermediate values	Central jet, width greater than 65% of LVOT
<b>Left ventricular enlargement</b>	minimal	Moderate to severe left ventricular enlargement	Severe left ventricular enlargement
<b>Doppler vena contracta width (cm)</b>	Less than 0.3	0.3-0.69	> than or equal to 0.7
<b>Regurgitation fraction</b>	<30%	30-49%	> 50%

<b>Diastolic reversal in the descending aorta</b>	No or brief	Intermediate values	Holodiastolic flow reversal
---	-------------	---------------------	--------------------------------

### **Aortic Valve – Assess by Peak Gradient**

AS jet velocity: Antegrade systolic velocity across the aortic valve is measured using continuous wave Doppler from the apical 4-chamber view and the suprasternal view.

### **Aortic Valve – Assess by Color Doppler, Vena Contracta, and Diastolic Reversal in the Descending Aorta**

Color Doppler: Presence or absence of aortic regurgitation is assessed through parasternal long imaging of the aortic valve. Imaging of the regurgitant jet will be obtained by measuring proximal jet width just below the aortic valve, within 1cm of the valve. The maximal proximal jet width obtained and its ratio to the left ventricular outflow tract will be compared.

Diastolic Reversal: The presence and degree of diastolic reversal in the descending aorta will be obtained from suprasternal notch imaging. It is normal to observe a brief diastolic flow reversal in the aorta, but with increased aortic regurgitation both the duration and velocity of the reversal increase.

### Tricuspid Valve

	<b>Mild Tricuspid Stenosis</b>	<b>Moderate Tricuspid Stenosis</b>	<b>Severe Tricuspid Stenosis</b>
<b>Mean gradient (mmHg)</b>	Less than 5	Intermediate values	>5mmHg
<b>Valve area (cm<sup>2</sup>)</b>	Greater than 1.5	1.0-1.5	Less than 1.0

	<b>Mild Tricuspid Regurgitation</b>	<b>Moderate Tricuspid Regurgitation</b>	<b>Severe Tricuspid Regurgitation</b>
<b>Hepatic Vein flow</b>	Systolic dominance	Systolic blunting	Systolic reversal
<b>Doppler vena contracta width (cm)</b>	Less than 0.3	<0.7	> than or equal to 0.7

#### **Additional notes:**

##### **Tricuspid Valve – Assess by Mean Gradient**

Tricuspid valve stenosis will be graded present using continuous wave Doppler interrogation obtained from the apical 4-chamber view at end-expiration.

##### **Tricuspid Valve – Assess by Color Doppler, Vena Contracta, Hepatic Vein Flow**

Vena Contracta: The vena contracta will be imaged in high resolution, zoom views for the largest obtainable proximal jet size for measurements. Parasternal short-axis imaging will be used to obtain the width of the neck, or narrowest portion of the jet.

Hepatic Vein Flow: Pulsed wave interrogation of the hepatic veins will be used to help corroborate the severity of the tricuspid regurgitation.

### Pulmonary Valve

	<b>Mild Pulmonary Stenosis</b>	<b>Moderate Pulmonary Stenosis</b>	<b>Severe Pulmonary Stenosis</b>
<b>Jet velocity (m/s)</b>	Less than 3.0	3.0-4.0	>4.0 or maximum gradient > 60mmHg

### Pulmonary Valve

	<b>Mild Pulmonary Regurgitation</b>	<b>Moderate Pulmonary Regurgitation</b>	<b>Severe Pulmonary Regurgitation</b>
<b>Color Doppler</b>	Thin (usually < 10mm in length) with narrow origin	Intermediate	Usually large, with a wide origin; may be brief in duration
<b>RV size</b>	Normal	Normal or Dilated	Dilated
<b>Pulmonary Valve</b>	Normal	Normal or Abnormal	Abnormal

**Additional Notes:**

Pulmonary Valve – Assess by Peak Gradient

Pulmonary valve stenosis is graded by continuous wave Doppler interrogation obtained from the parasternal short view. The highest velocity obtained will be recorded for measurement.

Pulmonary Valve – Assess by Two-dimensional imaging and Color Doppler

There is insufficient data on quantification of pulmonary regurgitation. The evaluation will, therefore, be qualitative.

**Two-Dimensional Images:** Two-dimensional echocardiography will be used to assess right ventricular size and anatomy of the pulmonary valve. Images will be obtained from the parasternal view. Abnormalities in the pulmonary valve including cusp number, motion (doming or prolapse) or structure (hypoplasia, dysplasia, or absence of the valve) will be assessed. In addition, evaluation of the size of the right ventricle will be assessed qualitatively from the apical 4-chamber view.

**Color Doppler:** Presence and degree of pulmonary regurgitation will be assessed by color flow imaging in the parasternal long and parasternal short views.

### Additional Notes on Echo/Doppler measurements and calculations:10

**Left ventricular dimensions** measured on the parasternal long-axis view just beyond mitral valve tips.

- Left Ventricular End-diastole (LVIDd): Measure the vertical distance from the endocardium of the IVS to the endocardium of the Left ventricular posterior wall (VLPW) in end-diastole
- Left Ventricular End-systole (LVIDs): Measure the vertical distance from the endocardium of the IVS at the lowest point of the septal motion to the endocardium of the Left ventricular posterior wall (VLPW)
- Left Atrial End-systolic dimension (LA): measure the greatest vertical distance between the trailing edge of the posterior aortic wall and the anterior side of the posterior left atrial wall at end ventricular systole when the aorta is in its maximal anterior position.
- Aortic Root End-Diastolic Diameter (AoR): Measure the maximal opening of the aortic valve cusps during the initial part of ventricular systole, using the internal borders of the aortic cusp echoes.



## Appendices

Adapted <sup>6-9</sup> from:

6. Bonow RO, Carabello BA, Chatterjee K, de Leon AC, Jr., Faxon DP, Freed MD, et al. 2008 focused update incorporated into the ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to revise the 1998 guidelines for the management of patients with valvular heart disease). Endorsed by the Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *J Am Coll Cardiol*. 2008 Sep 23;52(13):e1-142.

7. Nishimura RA, Carabello BA, Faxon DP, Freed MD, Lytle BW, O'Gara PT, et al. ACC/AHA 2008 guideline update on valvular heart disease: focused update on infective endocarditis: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines endorsed by the Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *Catheter Cardiovasc Interv*. 2008 Sep 1;72(3):E1-12.

8. Zoghbi WA, Enriquez-Sarano M, Foster E, Grayburn PA, Kraft CD, Levine RA, et al. Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. *J Am Soc Echocardiogr*. 2003 Jul;16(7):777-802.

9. Baumgartner H, Hung J, Bermejo J, Chambers JB, Evangelista A, Griffin BP, et al. Echocardiographic assessment of valve stenosis: EAE/ASE recommendations for clinical practice. *Eur J Echocardiogr*. 2009 Jan;10(1):1-25.

10. The echocardiographers's pocket reference Terry Reynolds

## 6.7 MEDICATION

Q18-20

**NB**

**If patients are NOT on secondary prophylaxis and you will only be commencing the secondary prophylaxis at the current visit, the answer to the question, is patient on secondary prophylaxis is NO.**

**Adherence to therapy**

To calculate the percent of injections received for an individual:

- Record the number of injections PRESCRIBED for a full 12 months (e.g. the number of injections prescribed from January and December 2007 for a person on 4-weekly treatment = 13 )
- Count the number of injections RECEIVED during the 12 months (e.g. 10 injections may have been received)
- Calculate: the number of injections RECEIVED (10) divided by the number PRESCRIBED (13) and multiply by 100

$$(10 \div 13) \times 100 = 77\%$$

In this example, the person received 77% of prescribed injections in 2007.

**NOTES:**

**Receiving less than 80% of injections places an individual at a higher risk of recurrent ARF. Follow-up may be required.**

**If injections were prescribed for the full year but no injections were received, record 0%.**



6.8 HIV OPTIONAL QUESTIONS	Q21
<p align="center"><b>REVISED WHO CLINICAL STAGING OF HIV/AIDS FOR ADULTS AND ADOLESCENTS</b></p>	
<p>(Interim African Region version for persons aged 15 years or more with positive HIV antibody test or other laboratory evidence of HIV infection)</p>	
<p>Primary HIV infection</p> <p>Asymptomatic</p> <p>Acute retroviral syndrome</p> <p><u>Clinical stage 1</u></p> <p>Asymptomatic</p> <p>Persistent generalised lymphadenopathy (PGL)</p>	
<p><u>Clinical stage 2</u></p> <p>Moderate unexplained weight loss (&lt;10% of presumed or measured body weight)</p> <p>Recurrent respiratory tract infections (RTIs, sinusitis, bronchitis, otitis media, pharyngitis)</p> <p>Herpes zoster</p> <p>Angular cheilitis</p> <p>Recurrent oral ulcerations</p> <p>Papular pruritic eruptions</p> <p>Seborrhoeic dermatitis</p> <p>Fungal nail infections of fingers</p>	

Clinical stage 3

Conditions where a presumptive diagnosis can be made on the basis of clinical signs or simple investigations

Severe weight loss (>10% of presumed or measured body weight)

Unexplained chronic diarrhoea for longer than one month

Unexplained persistent fever (intermittent or constant for longer than one month)

Oral candidiasis

Oral hairy leukoplakia

Pulmonary tuberculosis (TB) diagnosed in last two years

Severe presumed bacterial infections (e.g. pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, bacteraemia)

Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis

Clinical stage 4

Conditions where a presumptive diagnosis can be made on the basis of clinical signs or simple investigations HIV wasting syndrome

Pneumocystis pneumonia

Recurrent severe or radiological bacterial pneumonia

Chronic herpes simplex infection (orolabial, genital or anorectal of more than one month's duration)

Oesophageal candidiasis

Extrapulmonary TB

Kaposi's sarcoma

Central nervous system (CNS) toxoplasmosis

HIV encephalopathy

Conditions where confirmatory diagnostic testing is necessary:

Extrapulmonary cryptococcosis including meningitis

Disseminated non-tuberculous mycobacteria infection

Progressive multifocal leukoencephalopathy (PML)

Candida of trachea, bronchi or lungs

Cryptosporidiosis

Isosporiasis

Visceral herpes simplex infection

Cytomegalovirus (CMV) infection (retinitis or of an organ other than liver, spleen or lymph nodes)

Any disseminated mycosis (e.g. histoplasmosis, coccidiomycosis, penicilliosis)

Recurrent non-typhoidal salmonella septicaemia

Lymphoma (cerebral or B cell non-Hodgkin)

Invasive cervical carcinoma  Visceral leishmaniasis
---

## 7. FOLLOW-UP FORM

This form is completed after 12 months and then again after 24 months. It is clear that an exact period of 12 or 24 months may not be possible. We suggest attempting to conduct the follow-up interview with patients within a 3 month grace period. If more than 3 months has passed, we can still complete the follow-up form although these data may not be included under the 12 mth follow-up data.

If the patient does not complete the follow-up visit, attempt to complete via telephone or information via a third party. It is important to fill in the date that this information was obtained.

In particular:

- Update all contact details and ensure that new details are obtained if patient has relocated.
- If a patient refuses or cannot continue participation, e.g. with relocation, attempt to maintain telephone contact
- Ensure that all events have been captured relating to the previous 12 months. Source documents will be outlined in the relevant event forms and need to accompany the followup form.

## 8. EVENT DEFINITIONS

12	Congestive Cardiac Failure
13	Stroke
14	Hospitalisation
15	Major bleeding
16	Infective endocarditis
17	Prosthetic Valve Thrombosis
18	ARF
20	Valvuloplasty
21	Valve surgery
22	Atrial Fibrillation
23	Systemic embolism
19	Pregnancy
	Death

**Each of these events has the first 2 digits prespecified and filled in to the CRF. A patient with multiple events will be completed as follows: e.g.**

First episode of Stroke# 1301

First hospitalisation for above stroke #1401

Then surgery # 2101 Hospitalisation for surgery # 1402

Finally ARF # 1801 Hospitalisation for the ARF #1403

i.e. numerous repeat events are numbered sequentially, each entirely new event gets a new number.

5. Events: (As taken from doctor's notes and patient's recollection)

	No	Yes	Number of Episodes	Report#	Report#
a) Congestive Heart Failure	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="text"/> 1 <input type="text"/> 2 <input type="text"/> <input type="text"/>	<input type="text"/> 1 <input type="text"/> 2 <input type="text"/> <input type="text"/>
b) Stroke/TIA	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="text"/> 1 <input type="text"/> 3 <input type="text"/> <input type="text"/>	<input type="text"/> 1 <input type="text"/> 3 <input type="text"/> <input type="text"/>
c) Hospitalization	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="text"/> 1 <input type="text"/> 4 <input type="text"/> <input type="text"/>	<input type="text"/> 1 <input type="text"/> 4 <input type="text"/> <input type="text"/>
d) Major Bleeding	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="text"/> 1 <input type="text"/> 5 <input type="text"/> <input type="text"/>	<input type="text"/> 1 <input type="text"/> 5 <input type="text"/> <input type="text"/>
e) Infective endocarditis	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="text"/> 1 <input type="text"/> 6 <input type="text"/> <input type="text"/>	<input type="text"/> 1 <input type="text"/> 6 <input type="text"/> <input type="text"/>
f) Prosthetic Valve Thrombosis	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="text"/> 1 <input type="text"/> 7 <input type="text"/> <input type="text"/>	<input type="text"/> 1 <input type="text"/> 7 <input type="text"/> <input type="text"/>
g) Acute Rheumatic Fever	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="text"/> 1 <input type="text"/> 8 <input type="text"/> <input type="text"/>	<input type="text"/> 1 <input type="text"/> 8 <input type="text"/> <input type="text"/>
h) Valvuloplasty	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="text"/> 2 <input type="text"/> 0 <input type="text"/> <input type="text"/>	<input type="text"/> 2 <input type="text"/> 0 <input type="text"/> <input type="text"/>
i) Valve surgery	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="text"/> 2 <input type="text"/> 1 <input type="text"/> <input type="text"/>	<input type="text"/> 2 <input type="text"/> 1 <input type="text"/> <input type="text"/>
j) Systemic embolism	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="text"/> 2 <input type="text"/> 3 <input type="text"/> <input type="text"/>	<input type="text"/> 2 <input type="text"/> 3 <input type="text"/> <input type="text"/>
k) Atrial Fibrillation / Flutter	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="text"/> 2 <input type="text"/> 2 <input type="text"/> <input type="text"/>	<input type="text"/> 2 <input type="text"/> 2 <input type="text"/> <input type="text"/>

**Table Event definitions**

Outcome	Definition
Death	Death due to any cause
Congestive heart failure	Any 2 of the 3 following criteria: (i) signs (rales, increased jugular venous pressure or ankle edema) or symptoms (dyspnea on exertion or at rest, orthopnea, nocturnal paroxysmal dyspnea, or ankle edema) of congestive heart failure, (ii) radiological signs of pulmonary congestion, (iii) treatment with diuretics
Stroke	Diagnosis of stroke by a physician based on sudden onset of neurological deficit consistent with ischemia/infarction of a vascular territory, lasting 24 hours or more, with or without confirmation by neuroimaging
Transient ischemic attack	Deficits diagnosed by a physician lasting <24 hours
Non-CNS systemic embolism	Diagnosed clinically in patients with loss of arterial pulse and/or evidence of end-organ ischemia (e.g. ischemic limb pain, gangrene, etc.) with or without confirmation by Doppler studies or arteriography
Major bleeding	Bleeding that, (i) is fatal, (ii) involves a critical site (intracranial, retroperitoneal, intraspinal, intra ocular, pericardial, or intra-articular), or, (iii) leads to a reduction in haemoglobin 2 g/dl or more, or requires transfusion of two or more units of whole blood or packed red cells
New onset atrial fibrillation or flutter	Physician diagnosis with or without ECG evidence of atrial fibrillation or flutter
Acute rheumatic fever	Diagnosed by the current WHO criteria
Infective endocarditis	Diagnosed by the modified Duke criteria
Valve surgery	Performance of any valve repair, or replacement of valve with a tissue or mechanical prosthesis
Percutaneous valvular interventions	Percutaneous balloon dilatation of stenosed mitral, aortic or tricuspid valves
Prosthetic valve thrombosis	Recent onset ( $\leq 2$ weeks) symptoms of valve dysfunction (dyspnea, angina or congestive heart failure) accompanied by new onset of restricted valve leaflet motion on cinefluoroscopy with or without increased valve gradients on Doppler echocardiography

## 9. EVENT FORMS

### 9.1 REPORT NO 12 CONGESTIVE HEART FAILURE.

This should be completed for every NEW diagnosis of congestive heart failure, pulmonary oedema or both during the study period.

The date of onset should NOT be the same date as the follow-up appointment UNLESS the diagnosis HAS only been made at that appointment. If the patient was hospitalised, a Hospitalisation report form should also be completed.

### 9.2 REPORT NO 13 STROKE/TIA

Chose only one: either stroke or TIA

Stroke Diagnosis of stroke by a physician based on sudden onset of neurological deficit consistent with ischemia/infarction of a vascular territory, lasting 24 hours or more, with or without confirmation by neuroimaging

OR

Transient ischemic attack      Deficits diagnosed by a physician lasting <24 hours

Estimated date (e.g. month) and Time can suffice. Date of Diagnosis onset should be left OUT if unknown.

The difference in Q2 and Q4 is to appreciate any recovery that may have occurred over the study period.

### 9.3 REPORT 14 HOSPITALISATION

Hospitalisation is defined as being admitted to hospital for 24 hours or longer.

If patients were admitted to another hospital or institution for longer than 24 hours, this also counts as an event. Please attempt to obtain source documents and retain copies at the site office.

### 9.4 REPORT NO 15 MAJOR **BLEEDING**

Please attempt to complete Q1 as fully as possible. Source documents relating to INR values (Q4) should be retained at site.



#### 9.5 REPORT NO 16 **INFECTIVE** ENDOCARDITIS

This event form should be completed if infective endocarditis is strongly suspected or if participant is admitted with a presumptive diagnosis of infective endocarditis, regardless if a causative organism is not detected.

#### 9.6 REPORT 17 **PROSTHETIC** VALVE THROMBOSIS

Q1 refers to the diagnosis of prosthetic valve thrombosis.

Q6: unknown should be crossed off if no details of the index valve replacement are available.

Q10. If participant had pulmonary oedema, a congestive heart failure event from should also be completed.

#### 9.7 REPORT 18 **ACUTE** RHEUMATIC FEVER

<b>Diagnostic categories</b>	<b>Criteria</b>
Primary episode of RF	Two major or one major and two minor manifestation <b>PLUS</b> evidence of a preceding group A streptococcal infection
Recurrent attack of RF in a patient without established rheumatic heart disease	Two major or one major and two minor manifestation <b>PLUS</b> evidence of a preceding group A streptococcal infection
Recurrent attack of RF in a patient with established rheumatic heart disease	Two minor manifestation <b>PLUS</b> evidence of a preceding group A streptococcal infection
Rheumatic chorea Insidious onset rheumatic carditis	Other major manifestation <b>or</b> evidence of a preceding group A streptococcal infection not required
<b>Major manifestations</b>	Carditis Polyarthritis Chorea Erythema marginatum Subcutaneous nodules
<b>Minor manifestations</b>	Clinical: fever, polyarthralgia Laboratory: Elevated acute phase reactants (ESR, CRP, WCC)
<b>Supporting evidence of a preceding streptococcal infection within the past 45 days</b>	ECG: Prolonged PR interval Elevated or raising antistreptolysin-O or other streptococcal antibody <b>OR</b> a positive throat culture <b>OR</b> rapid antigen test for GAS or recent scarlet fever

Taken from:

2002-2003 WHO criteria for the diagnosis of rheumatic fever and rheumatic heart disease  
(based on the revised Jones criteria) WHO technical series

Please note that Carditis as a major criterion includes endocarditis, pericarditis and myocarditis. Echo-confirmed valvular regurgitation is NOT a pre-requisite for the diagnosis of rheumatic carditis. However for the purposes of REMEDY – participants with the diagnosis of ARF but a normal heart (i.e., diagnosis of ARF made upon other criteria), are NOT included. RHEUMATIC HEART DISEASE is the pre-requisite condition for entry into REMEDY.

#### 9.8 REPORT NO 20 **VALVULOPLASTY**

Wilkins GT, Weyman AE, Abascal VM, Block PC, Palacios I. Percutaneous balloon dilatation of the mitral valve: an analysis of echocardiographic variables related to outcome and the mechanism of dilatation. Br Heart J 1988;60:299.

<b>Leaflet mobility</b>	<b>1</b>	Highly mobile valve with only leaflet tips restricted
	<b>2</b>	Leaflet mid and base portions have normal mobility
	<b>3</b>	Valve continues to move forward in diastole, mainly from the base
	<b>4</b>	No or minimal forward movement of the leaflets in diastole
<b>Leaflet thickening</b>	<b>1</b>	Leaflets near normal in thickness (4-5 mm)
	<b>2</b>	Mid-leaflets normal, considerable thickening of margins (5-8 mm)
	<b>3</b>	Thickening extending through the entire leaflet (5-8 mm)
	<b>4</b>	Considerable thickening of all leaflet tissue (>8-10 mm)

<b>Leaflet calcification</b>	<b>1</b>	A single area of increased echo brightness
	<b>2</b>	Scattered areas of brightness confined to leaflet margins
	<b>3</b>	Brightness extending into the mid-portion of the leaflets
	<b>4</b>	Extensive brightness throughout much of the leaflet tissue
<b>Subvalvular thickening</b>	<b>1</b>	Minimal thickening just below the mitral leaflets
	<b>2</b>	Thickening of chordal structures extending up to one third of the chordal length
	<b>3</b>	Thickening extending to the distal third of the chords
	<b>4</b>	Extensive thickening and shortening of all chordal structures extending down to the papillary muscles

Please complete any relevant additional event from if indicated under Q5.

## 9.9 **REPORT** NO 21 VALVE SURGERY

These indications are adapted from the following references:

1. <http://www.ncbi.nlm.nih.gov/pubmed/18848134?dopt=Citation>

J Am Coll Cardiol. 2008 Sep 23;52(13):e1-142.

2008 focused update incorporated into the ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to revise the 1998 guidelines for the management of patients with valvular heart disease). Endorsed by the Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons.

Bonow RO et al; American College of Cardiology/American Heart Association Task Force on Practice Guidelines

2. <http://www.escardio.org/guidelines-surveys/esc-guidelines/GuidelinesDocuments/guidelinesVHD-FT.pdf>

Guidelines on the management of valvular heart disease: The Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology.

Vahanian A et al. Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology; ESC Committee for Practice Guidelines.

Eur Heart J. 2007 Jan;28(2):230-68. Epub 2007 Jan 26

#### 9.10 **REPORT** NO 23 SYSTEMIC EMBOLISM

Please complete any relevant additional event form if indicated under Q5 and 11.

#### 9.11 REPORT NO 22 ATRIAL FIB/FLUTTER

Please complete any relevant additional event form if indicated under Q6. Source documents can be retained at site.

#### 9.12 **REPORT** NO 19 PREGNANCY

Q C Parity: gravidity is defined as the number of times that a woman has been pregnant and parity is defined as the number of times that she has given birth to a fetus with a gestational age of 24 weeks or more, regardless of whether the child was born alive or was stillborn. ie multiple birth would be G1 P2 (one pregnancy 2 babies) and 2 miscarriages would be G2P0. Please note as this system may be different in different regions.

#### 9.13 DEATH

If additional information is needed under Q4, please supply this and retain documents at site.

#### 9.14 FINAL **POINTS** REGARDING ALL CRFS

These report forms have been constructed in such a way as to reflect current evidence-based practice. There may of course be significant geographical differences and we do anticipate problems in the Vanguard stage of this study. Any problems, concerns, difficulties will be addressed in future versions of the forms and therefore your input/comments and ideas are greatly appreciated. These should be directed at [liesl.zuhlke@uct.ac.za](mailto:liesl.zuhlke@uct.ac.za) in the first instance.

**Primary Outcomes**

- Death
- Recurrence of ARF
- Worsening heart failure
- Stroke
- Systemic embolism
- Major bleeding
- Occurrence of other complications such as infective endocarditis and
- Prosthetic valve thrombosis

**Additional Objectives**

**Describe**

- Patterns and severity of valve involvement
- Prevalence of AF and other co-morbid conditions
- The pharmacological treatments used, particularly secondary prophylaxis, oral anticoagulation therapy and anti-arrhythmic therapy for AF

**Identify**

- Barriers to adherence
- Risk factors for adverse outcomes

## 11.1 **ORGANISATION** AND GOVERNANCE

### Coordinators:

Mark Engel and Liesl Zühlke (African sites), and Ganesan Karthikeyan (Indian sites)

Responsibilities include:

- Day-to-day running of the registry under the supervision of the Steering Committee
- Keeping and disseminating the minutes of the Steering Committee.
- Preparation of the trial protocol, a master copy of the study materials and aids, development of the case record forms, study database, data internal consistency checks and data analysis.
- Preparation of the interim reports for the independent data safety and monitoring board
- Applications for research grants to fund the study.

Operations Committee: Liesl Zühlke (Chair), Mark Engel, Teo Koon, Sumathy Rangarajan, Bongani Mayosi

- It is responsible for monitoring the Registry's function on a short-term basis and for implementing decisions of the Steering Committee.
- The Operations Committee will meet every three months and its decisions and minutes will be circulated to all participants by means of a newsletter.

### The Steering Committee:

- The Steering Committee consists of the members of the Operations Committee and Site Principal Investigators. Bongani Mayosi (Chair).
- It is proposed that at least one member of the Steering Committee should be from each of the countries actively recruiting. In the case of large countries with active recruitment consideration will be given to sub-dividing countries on a regional or provincial basis for the purpose of representation. Countries and regions will be asked to nominate representatives to the Steering Committee and to vote to select the representative should there be more than one nominee.
- The Steering Committee is responsible for the overall policy of the Registry and for supervising its successful conclusion. Publication policy and sub-study policy are decided by the Steering Committee. Decisions of the Steering Committee will be communicated to all active participants by dissemination of its minutes through the regular newsletter.

- The Steering Committee will attempt to meet annually (dependent on finance). It is recognised that many meetings will be “opportunistic” and will be held at the time of national meetings which most members will attend. If this is not possible in any one year an international tele-conference will be held in its place.

## 11.2 **PUBLICATION** POLICY

- Publication policy and authorship will be co-ordinated through the **Publications Committee** that reports directly to the Steering Committee of which it is a subcommittee. Guidelines for the Publications Committee are as follows:
- **Ganesan Karthikeyan** will chair the Publications Committee and will be responsible for selecting, through a process of consultation with members of the Steering Committee, three other members who will constitute the Publications Committee.
- The overall purpose of the Publications Committee is to:
- Ensure the timely writing and publication of high quality manuscripts from Registry data;
- Solicit, review and prioritise analysis plans and manuscripts from the Registry database;
- Prioritise authorship of manuscripts / abstracts / posters arising from the Registry database in a fair and just manner;
- Review manuscripts / abstracts / posters arising from the Registry database.

## 11.3 AUTHORSHIP GUIDELINES

- *Primary Publications:* it is anticipated that at least two primary publications should result if the registry is successful. The first (methods) will describe the rationale, design and methodology of the registry. The second (results) will describe the outcome of the registry. Authorship of the primary publications will be in the name of the global registry of RHD – pilot study. All actively recruiting centres will be listed in an appendix under the name of the principal investigator and his / her organisational affiliation.
- *Secondary Publications:* These may arise from sub-studies or from suggestions from participants who wish to analyse the Registry database in areas of personal interest. In such instances the **Publications Committee** will be responsible for ensuring that first and last authors are the people that have developed the project idea and done the writing and also for ensuring that all listed authors meet conventionally accepted authorship credit guidelines. Co-ordinating centre workers may be included as authors at the discretion of the **Publications Committee**.

## 11.4 SUB-STUDIES



## Appendices

- Actively recruiting centres and investigators are encouraged to propose sub-studies and sub-analyses of the data in the Registry database.
- A Sub-study Committee (**Chair: Mark Engel**), which reports to the Steering Committee, will review all such proposals to ensure that they are feasible and do not compromise the integrity of the database and primary publications.
- Proposed sub-studies:
  - Genetics
  - Barriers to Adherence to Secondary Prophylaxis
  - Paediatric Sub-analysis

### 11.5 MEMORANDUM OF AGREEMENT

- Signed after ethics approval has been obtained
- Outline site specific deliverables
- Confirm the arrangement and details for the transfer of funds to the site

Constitutes the formal statement of joining the Global Registry of RHD as Principal Investigator and Contributing Site

### 11.6 PROJECT COORDINATING OFFICE:

Department of Medicine, Groote Schuur Hospital, University of Cape Town, South Africa.

Responsibilities include:

- Ensuring good collaboration with the study sites.
- Assisting sites in obtaining ethical & regulatory approvals
- Preparation and distribution of study materials and study aids.
- Monitoring distribution of study medication to study sites.
- Receiving CRFs and other relevant material from study sites.
- Data entry, data validation and quality control checks.
- Organisation of Investigator's meetings

- Communication help lines
- Monitoring of study sites
- Payments to sites
- Preparation and distribution of study updates
- Assisting sites with smooth running of the study
- Training site teams on study procedures

## 11.7 INVESTIGATING SITES

### RESPONSIBILITIES INCLUDE:

- Forming the ASAP global registry team and raise awareness among all medical and nursing staff involved in the care of rheumatic heart disease patients.
- Obtaining ethics and other regulatory approvals.
- Ensuring that all patients admitted with a diagnosis of rheumatic heart disease are considered for screening for the trial, making sure that all eligible consenting patients are enrolled.
- Completing all necessary Case Report Forms for that particular visit and sending them promptly to the Project Coordinating Office.
- Responding promptly to all inquiries from the Project Coordinating Office regarding patient CRFs, Event forms etc. or other important study matters.
- Participating in monitoring visits by responding to all queries raised.

## 11.8 MAINTENANCE OF RECORDS

### The Principal Investigator must:

- Maintain a Screening Log of all patients with rheumatic heart disease considered for enrollment.
- Make sure that all patients folders and related all documents are kept in an office in a securely locked cabinet, and accessible to study staff.

## Appendices

- Obtain a correctly completed Patient Informed Consent Form for each patient enrolled into the study.
- Maintain a list of Patient ID and corresponding patient names to enable records to be found at a later date (this should be kept in a locked cabinet away from CRFs to maintain blinding).
- Retain all records, including the signed Informed Consent Forms and the Patient Identification List for **at least 2 years** after the official study closeout.

The PCO will inform the Investigator when these documents no longer need to be retained.

### 11.9 **COMMUNICATION**

The first line of contact for study related questions would be the Project Coordinating Office.

#### **Contacts**

##### **PROJECT COORDINATING OFFICE**

Department of Medicine

H47, Old Main Building

Groote Schuur Hospital University of

Cape Town

##### **CANADIAN INTERNATIONAL COLLABORATORS**

Population Health Research Institute

Hamilton General Hospital

237 Barton Street East

Mac Clinic, 2<sup>nd</sup> Floor, Room 252

Hamilton, Ontario L8L 2X2

CANADA

Tel: +905-527-4322

Fax: +905-521-1166

## 12. REFERENCES

1. The Criteria Committee of the New York Heart Association. 9th ed. Boston MA, Brown & Co; . Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 1994: 253-6.
2. TRENTON D. NAUSER MD, and STEVEN W. STITES, M. Diagnosis and Treatment of Pulmonary Hypertension. *Am Fam Physician*. 2001; **May 1**(63(9)): 1789-99.
3. Prendergast BD. Diagnosis of infective endocarditis. *BMJ*. 2002; **325**(7369): 845-6.
4. Baddour LM, Wilson WR, Bayer AS, Fowler VG, Jr., Bolger AF, Levison ME, et al. Infective endocarditis: diagnosis, antimicrobial therapy, and management of complications: a statement for healthcare professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, and the Councils on Clinical Cardiology, Stroke, and Cardiovascular Surgery and Anesthesia, American Heart Association: endorsed by the Infectious Diseases Society of America. *Circulation*. 2005; **111**(23): e394-434.
5. McKee PA CW, McNamara PM, Kannel WB. The natural history of congestive heart failure: the Framingham study. *N Engl J Med*. 1971; **Dec 23**; **285**(26): 1441-6.
6. Bonow RO, Carabello BA, Chatterjee K, de Leon AC, Jr., Faxon DP, Freed MD, et al. 2008 focused update incorporated into the ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to revise the 1998 guidelines for the management of patients with valvular heart disease). Endorsed by the Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *J Am Coll Cardiol*. 2008; **52**(13): e1-142.
7. Nishimura RA, Carabello BA, Faxon DP, Freed MD, Lytle BW, O'Gara PT, et al. ACC/AHA 2008 guideline update on valvular heart disease: focused update on infective endocarditis: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines endorsed by the Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *Catheter Cardiovasc Interv*. 2008; **72**(3): E1-12.
8. Zoghbi WA, Enriquez-Sarano M, Foster E, Grayburn PA, Kraft CD, Levine RA, et al. Recommendations for evaluation of the severity of native valvular regurgitation with twodimensional and Doppler echocardiography. *J Am Soc Echocardiogr*. 2003; **16**(7): 777-802.
9. Baumgartner H, Hung J, Bermejo J, Chambers JB, Evangelista A, Griffin BP, et al. Echocardiographic assessment of valve stenosis: EAE/ASE recommendations for clinical practice. *Eur J Echocardiogr*. 2009; **10**(1): 1-25.
10. Li JS, Sexton DJ, Mick N, Nettles R, Fowler VG, Ryan T, et al. Proposed Modifications to the Duke Criteria for the Diagnosis of Infective Endocarditis. *Clinical Infectious Diseases*. 2000; **30**(4): 633-8.
11. Karthikeyan G, Math RS, Mathew N, Shankar B, Kalaivani M, Singh S, et al. Accelerated infusion of streptokinase for the treatment of left-sided prosthetic valve thrombosis: a randomized controlled trial. *Circulation*. 2009; **120**(12): 1108-14.

### Consent **Form**

#### 1. STATEMENT BY THE PERSON AGREEING TO PARTICIPATE IN THIS STUDY

I have read this Participant Information Sheet and informed consent document describing the benefits, risks and procedures for the research study titled "Global Registry of Rheumatic Heart Disease in Cape Town, South Africa" or it was read and explained to me. I freely and voluntarily choose to participate in the study.

Name of participant: \_\_\_\_\_

\_\_\_\_\_

Date

\_\_\_\_\_  
Signature or thumbprint of participant

#### 2. IF THE PARENT/GUARDIAN CANNOT READ THE FORM THEMSELVES, A WITNESS MUST SIGN HERE:

I was present while the informed consent document with benefits, risks and procedures were read to the parent/guardian and the participant. The parent/guardian has freely and voluntarily agreed to allow her/his daughter/son to take part in the research.

\_\_\_\_\_

Date

\_\_\_\_\_

Signature of witness

#### 3. STATEMENT BY PARENT/GUARDIAN AGREEING FOR HIS/HER CHILD TO PARTICIPATE IN THIS STUDY

I have read this Participant Information Sheet and informed consent document describing the benefits, risks and procedures for the research study titled "Global Registry of Rheumatic Heart Disease in Cape Town, South Africa" or it was read to me. I freely and voluntarily choose to allow my son/daughter to participate in the study.

Name of child participant: \_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_  
Date Signature or thumbprint of parent/guardian

**Principal Investigator:**

Bongani M. Mayosi, D.Phil. Groote Schuur Hospital  
Tel: 27-21-406-6200 [bongani.mayosi@uct.ac.za]

**Concerns or Complaints:**

Human Research Ethics Committee  
(021) 406-6338.

Assent **Form** for Children 8 years and older

We are doctors and nurses from Red Cross Children's, Groote Schuur Hospitals and Tygerberg Hospitals and we are doing a study of hearts of children with rheumatic heart disease.

We would like to ask you a few questions about your health. This will not hurt at all and is very quick.

If you agree to take part in this study, you will be helping doctors to know how better to treat other children in the future.

You are allowed to say that you don't want to be in the study. Nobody will be angry with you if you say no.

Before you decide, you can ask us questions. If you want to be in the study, you must write your name on this sheet of paper. This means that you are happy to be involved in the study.

**Child Participant:**


---

 Printed name

Signature

Date

**Study doctor or research nurse:**


---

 Printed name

Signature

Date

**Witness:**


---

 Printed name

Signature

Date

<b>Principal Investigator:</b> Bongani M. Mayosi, D.Phil. Groote Schuur Hospital Tel: 27-21-406-6200 [bongani.mayosi@uct.ac.za]	<b>Concerns or Complaints:</b> Human Research Ethics Committee (021) 406-6338.
---	--